# Exhibit 19

**UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK**

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| **IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation**<br><br>**This Document Relates to: All Actions** | **Docket No.: 22-md-3043 (DLC)** |

**AMENDED EXPERT REPORT OF STEPHEN V. FARAONE, Ph.D.**

# AMENDED EXPERT REPORT OF STEPHEN V. FARAONE, Ph.D.

## I.

## INTRODUCTION AND SUMMARY OF OPINIONS

1. I am Distinguished Professor in the Departments of Psychiatry and Neuroscience & Physiology at the State University of New York (SUNY) Upstate Medical University and Vice Chair for Research in the Department of Psychiatry and Behavioral Sciences. I am Senior Scientific Advisor to the Research Program on Pediatric Psychopharmacology at Massachusetts General Hospital and a lecturer at Harvard Medical School. For more than 30 years, I have performed original research on the diagnosis, etiology, and pathophysiology of Attention Deficit/Hyperactivity Disorder (ADHD), and I have published more than 840 articles on ADHD. In 2019, I was elected President of the World Federation of ADHD and in 2023 was re-elected to that position. In 2021, I coordinated the creation and publication of the World Federation of ADHD International Consensus Statement on ADHD.

2. ADHD is a chronic neurodevelopmental psychiatric disorder that starts in childhood and can continue through adulthood. Diagnostic criteria are based on two core symptom domains: inattention and hyperactivity-impulsivity. For the inattention presentation, the child must exhibit six or more symptoms of inattention. For the hyperactive-impulsive presentation, the child must exhibit six or more symptoms of hyperactivity or impulsivity that are disruptive. For both presentations, the symptoms must be inappropriate for the child's developmental level and persist for at least six months. A diagnosis of ADHD also requires that several symptoms be present before age 12, that symptoms be present in two or more settings (e.g., home and school), that the symptoms interfere with social functioning, and that the symptoms not be better explained by another mental disorder.

3. ADHD can only be diagnosed by a licensed clinician who interviews the parent, caregiver and/or patient to document criteria for the disorder. It cannot be diagnosed by rating scales alone, biomedical laboratory tests, neuropsychological tests, or methods for imaging the brain. Professional associations have endorsed and published guidelines for diagnosing ADHD.

4. ADHD occurs throughout the developed and developing world and is more common in males compared with females. It has not become more common over the past three decades, although, due to increased recognition by clinicians, the disorder is more likely to be diagnosed today than previously.

5. The changes in the brain associated with ADHD are not entirely understood. Neuroimaging and neuropsychological studies reveal a wide variability of findings.

6. Genetics are considered the predominant cause of ADHD. When studies of proposed environmental risk factors for ADHD have used study designs that account for the role of familial/genetic liability (i.e., sibling control designs), the elevated risks have disappeared.

7. There is no reliable scientific evidence that maternal use of acetaminophen causes ADHD in offspring. Although more than 20 epidemiological studies have been published, they do not support a causal inference.

- Approximately half of the epidemiological studies evaluate scores on questionnaires that only provide crude approximations of some ADHD symptoms and do not capture the criteria required to diagnose ADHD.
- The studies that use ADHD diagnoses reported low risk estimates, which are likely due to residual confounding, including genetic confounding. (Confounding refers

to a circumstance where an unmeasured, alternative factor is responsible for an observed increase in risk, rather than the exposure that is being studied.)

- The application of sibling control design, which accounts for familial and genetic confounders, effectively eliminated any proposed association between prenatal use of acetaminophen and ADHD in offspring in the one study that used this design.

8. Although the epidemiological data do not support a finding of an association that is free from bias, confounding, and chance, I nevertheless examined the published scientific data using the framework described by Bradford Hill. These criteria do not support a causal inference. Strength of association is not satisfied because the reported associations are weak and influenced by confounding. The study results are inconsistent across different populations and measures. Many of the reported associations are not specific to ADHD. There is no clear dose response reported in the literature. And the association is not biologically plausible because there is no known pathophysiological mechanism of injury for the development of ADHD. Although rodent studies can help inform hypotheses about the etiology of ADHD, they cannot support causal inferences because ADHD cannot be diagnosed in rodents.

9. My analysis is consistent with statements issued by public health organizations in the fields of obstetrics/gynecology and maternal fetal medicine, which have addressed the hypothesis that acetaminophen exposure during pregnancy causes neurodevelopmental disorders, including ADHD, in offspring. These include (a) the American College of Obstetricians and Gynecologists, which has stated that the literature "show[s] no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any

trimester and fetal developmental issues,"[1] (b) the Society of Obstetricians and Gynaecologists of Canada, which has stated "that the evidence for causality for this claim is weak and has many fundamental flaws,"[2] (c) the Society for Maternal-Fetal Medicine, which has stated "that the weight of evidence is inconclusive regarding a possible causal relationship between acetaminophen use and neurobehavioral disorders in the offspring" and "continue[d] to advise that acetaminophen be considered a reasonable and appropriate medication choice for the treatment of pain and/or fever during pregnancy,"[3] (d) the Royal College of Obstetricians and Gynaecologists, which has stated that acetaminophen "is considered safe for use throughout pregnancy,"[4] and (e) the European Network of Teratology Information Services, which has stated that the "evidence brought forward [in favor of the hypothesis] is weak, inconsistent and to a large extent fundamentally flawed."[5]

10. Regulatory agencies have also addressed the data. In 2019, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency stated: "A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results."[6] In 2020, the United States Food and Drug Administration (FDA) "found all of the studies [it] reviewed to have potential limitations in their designs" and "sometimes the

[1] American College of Obstetricians and Gynecologists, *ACOG Response to Consensus Statement on Paracetamol Use During Pregnancy* (Sept. 29, 2021).

[2] Janine R. Hutson et al., *Statement on the Use of Acetaminophen for Analgesia and Fever in Pregnancy* (Nov. 8, 2021).

[3] Society for Maternal-Fetal Medicine Publications Committee, *Prenatal Acetaminophen Use and Outcomes in Children*, at B15 (Mar. 2017).

[4] Bisson, D. L. (2018). Antenatal and postnatal analgesia: Scientific Impact Paper No. 59. *BJOG*, e117-118.

[5] European Network of Teratology Information Services, *Position Statement on Acetaminophen (Paracetamol) in Pregnancy*, at 2 (Oct. 3, 2021).

[6] European Medicines Agency, *PRAC Recommendations on Signals Adopted At The 12-15 March 2019 PRAC Meeting*, at 4-5 (Apr. 8, 2019).

accumulated studies on a topic contained conflicting results that prevented [it] from drawing reliable conclusions."[7]

11. I have reviewed the reports of plaintiffs' experts Stan G. Louie, Pharm. D., Eric Hollander, M.D., Brandon Pearson, M.S., Ph.D., Robert M. Cabrera, Ph.D., and Andrea Baccarelli, M.D., Ph.D., M.P.H. I have also reviewed the supplemental reports of plaintiffs' experts Brandon Pearson, M.S., Ph.D. and Robert M. Cabrera, Ph.D. These reports do not change my assessment of the evidence and do not refute the conclusions reached by multiple organizations rejecting the hypothesis that maternal use of acetaminophen during pregnancy causes ADHD in offspring.

## II.

## QUALIFICATIONS AND EXPERIENCE

12. I received my Ph.D. in Clinical Psychology from the University of Iowa in 1982, completed a clinical internship at Brown University in 1983, and completed a fellowship in psychiatric epidemiology and genetics at Brown University in 1984. From 1985 to 2004, I was on the faculty of Harvard Medical School, where I was promoted to Professor. Between 2003 and 2004, I was also Professor in the Department of Epidemiology at Harvard's School of Public Health.

13. In 2004, I joined the faculty of SUNY Upstate Medical University, where I am currently Vice Chair for Research in the Department of Psychiatry and Behavioral Sciences. In 2013, I was given the title of Distinguished Professor at SUNY for the national and international recognition of my achievements in the field of child and adolescent mental health.

[7] FDA, *FDA Drug Safety Communication: FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy* (Jan. 9, 2015).

14. I have authored or co-authored over 1,000 journal articles, editorials, chapters, and books. Between 1990 and 1999, I was the eighth highest producer of High Impact Papers in Psychiatry, as determined by the Institute for Scientific Information (ISI).[8] In 2005, I was ranked by ISI as the second highest cited author for ADHD.[9] Between 2014 and 2021, I was listed as a highly cited researcher by Thomson Reuters/Clarivate Analytics. Based on the impact of my publications from 2012 to 2023, I was ranked the top-rated expert for ADHD and for neurodevelopmental disorders worldwide.[10]

15. I am Editor for the journal *Neuropsychiatric Genetics*, and Program Director of a website that provides continuing education for health care professionals seeking to learn how to diagnose and treat ADHD in adults.[11] I also direct another website that provides evidence-based information about ADHD for the public.[12] I am President of the World Federation of ADHD and was a Founding Board member for the American Professional Society of ADHD and Related Disorders. I founded the ADHD Molecular Genetics Network in the 1990s and was a founding member of the Psychiatric Genomics Consortium's Coordinating Committee. I led the worldwide ADHD genetics group to complete the first genomewide association study of ADHD, which discovered the first genomic risk variants for ADHD. For that (and other contributions), I was awarded the Lifetime Achievement Award from the International Society of Psychiatric Genetics.

[8] Institute for Scientific Information, Science, 2000, Vol 288, p. 959.

[9] https://bit.ly/35Nk3Kc.

[10] https://bit.ly/3j9n8w2; https://www.research.com.

[11] www.adhdinadults.com.

[12] www.ADHDevidence.org.

16. I have been selected as a reviewer for many top journals in psychiatry, including *JAMA Psychiatry, Lancet Psychiatry, American Journal of Psychiatry, and Biological Psychiatry*. I have been a co-author on papers published in leading journals (e.g., *Science, New England Journal of Medicine*). I am often invited to give plenary talks on ADHD to professional organizations. For example, in 2023, I was invited to give plenary talks to the American Professional Society for ADHD and Related Disorders, the Norwegian Psychiatric Association and the Danish Psychiatric Association.

17. In 2002, I was inducted into the Children and Adults with Attention Deficit Disorder Hall of Fame in recognition of outstanding achievement in medicine and education research on attention disorders. In 2008, I received the SUNY Upstate President's Award for Excellence and Leadership in Research. In 2009, I was awarded Alumni Fellow status at the University of Iowa in recognition of my contributions to society and my profession. In 2010, I received the Chancellor's Award for Excellence in Scholarship and Creative Activities from SUNY. In 2018, I received the Lifetime Achievement Award from the International Society of Psychiatric Genetics. In 2019, I received the Paul Hoch Award from the American Psychopathological Association.

18. Over the course of my career, I have received funding from the U.S. National Institutes of Health, the European Union and other agencies, totaling over $25,000,000. I am frequently asked to consult with or join the scientific advisory boards of companies that create and manufacture treatments for ADHD (Noven, Axsome Supernus, Arbor, Tris, Aardvark, Aardwolf, Shire, Rhodes, Ironshore, Enzymotec, Neurovance, Alcobra, Sunovion, Rhodes, KemPharm/Corium, Enzymotec, Neurolifesciences, Takeda, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly) or devices for ADHD (CogCubed, Akili, Atentiv, OnDosis, and Sky

Therapeutics). I am also on the scientific advisory board of Genomind, which develops pharmacogenetic tests for ADHD and other disorders.

19. My *curriculum vitae* sets forth a complete list of my education, training, and professional experience.

## III.

## ATTENTION DEFICIT / HYPERACTIVITY DISORDER

20. ADHD, also known as Hyperkinetic Disorder, is a common disorder with characteristic symptoms of inattention and/or hyperactivity and impulsivity. The disorder was first described by a German physician in 1775.[13] In 1937, the efficacy of amphetamine for symptom reduction was discovered serendipitously. In the 1940s, the brain was implicated as the source of ADHD-like symptoms, which were observed following minimal brain damage in the wake of an encephalitis epidemic. In 1980, the third edition of the Diagnostic and Statistical Manual (DSM) created the first systematic, reliable diagnostic criteria for the disorder.[14]

### A. Diagnostic Criteria

21. Under the current definition, as set forth in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5), a diagnosis of ADHD requires a trained diagnostician to document that at least six symptoms of inattention and/or six symptoms of hyperactivity-impulsivity have been present for at least six months (only five symptoms in either category are required for those older than 16). These diagnostic criteria are

[13] Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., Rohde, L. A., Sonuga-Barke, E. J., Tannock, R. & Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers* 1, 15020.

[14] American Psychiatric Association (1980). *Diagnostic and Statistical Manual of Mental Disorders (3rd ed.)*. American Psychiatric Publishing.

listed in Table 1.[15] As these criteria indicate, one can be diagnosed with ADHD based on the presence of only hyperactive-impulsive symptoms, only inattentive symptoms or some mix of those symptoms. These are coded as the hyperactive-impulsive, inattentive and combined presentations. These are not considered "subtypes" because the presentations change over time.

| **Table 1 Diagnostic Criteria for ADHD in the Fifth Edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5)** |
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| **Inattention: Six or more symptoms of inattention for children up to age 16 years, or five or more for adolescents age 17 years and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level** |
| Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities. |
| Often has trouble holding attention on tasks or play activities. |
| Often does not seem to listen when spoken to directly. |
| Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked). |
| Often has trouble organizing tasks and activities. |
| Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework). |
| Often loses things necessary for tasks and activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones). |
| Is often easily distracted. |
| Is often forgetful in daily activities. |
| **Hyperactivity and Impulsivity: Six or more symptoms of hyperactivity-impulsivity for children up to age 16 years, or five or more for adolescents age 17 years and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level:** |
| Often fidgets with or taps hands or feet, or squirms in seat. |
| Often leaves seat in situations when remaining seated is expected. |
| Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless). |
| Often unable to play or take part in leisure activities quietly. |
| Is often "on the go" acting as if "driven by a motor." |
| Often talks excessively. |
| Often blurts out an answer before a question has been completed. |
| Often has trouble waiting their turn. |
| Often interrupts or intrudes on others (e.g., butts into conversations or games). |
| Note: Some symptoms and impairments must be present prior to age twelve. |

[15] American Psychiatric Association (2022). *Diagnostic and Statistical Manual of Mental Disorders (5th ed.) Text Revision*. American Psychiatric Publishing.

22. Because the behaviors listed above are present in many children to varying degrees, the DSM diagnosis of ADHD requires that three "qualifying criteria" must be met for the symptoms to be considered indicative of a disorder rather than normal development.[16] Thus, symptom counts can exceed the threshold but not be diagnostic for ADHD if the qualifying criteria are not achieved. These qualifying criteria must be addressed in a clinical interview with the parent and/or (for older children and adults) the patient.

23. The first qualifying issue is that the symptoms must be extreme for the child's developmental level. Age is usually a good proxy for "developmental level." For example, we expect a five-year-old to run around and climb on furniture more than a sixteen-year-old. Age is not a good proxy for some children, such as those with Down's Syndrome or Intellectual Disability, who do not develop at the rate typical for healthy children. To diagnose ADHD, trained clinicians must make judgments about the child's level of development. One reason why parent ratings made on questionnaires cannot be used to make a diagnosis is that parents have not been trained to know if their child's behavior is extreme for their developmental level.

24. The second qualifying issue is that the symptoms must cause impairment in more than one setting, such as home and school. If ADHD symptoms are present at home but not school (or vice-versa), the diagnostician would suspect that the symptoms are due to some environmental disruption in that setting. There are many types of impairments that can be attributed to ADHD. Examples include misbehaving at home or school, performing poorly on homework or tests, having difficulties socializing with other children, disrupting the classroom or

[16] American Psychiatric Association (2022). *Diagnostic and Statistical Manual of Mental Disorders (5th ed.) Text Revision*. American Psychiatric Publishing.

home environment, and getting into accidents due to not paying attention or to being impulsive. Omitting impairment from a diagnostic approach leads to false positive diagnoses of ADHD.[17]

25. The third qualifying issue is that putative symptoms of ADHD should not be better explained by another disorder. For example, sleep apnea and other somatic disorders can mimic ADHD, and treatment for sleep apnea can reduce those symptoms.[18]

**B. Diagnostic Process**

26. There is no biological test for ADHD, although many have been investigated.[19] Diagnosing the disorder relies on the clinician asking patients, parents, or other informants (sometimes teachers or other caregivers) about the symptoms of the disorder and

[17] Polanczyk, G., & Rohde, L. A. (2007). Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. *Current Opinion in Psychiatry*, *20*(4), 386-392.

Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*(6), 942-948.

Gordon, M., Antshel, K., Faraone, S., Barkley, R., Lewandowski, L., Hudziak, J. J., ... & Cunningham, C. (2006). Symptoms versus impairment: The case for respecting DSM-IV's Criterion D. *Journal of Attention Disorders*, *9*(3), 465-475.

Gathje, R. A., Lewandowski, L. J., & Gordon, M. (2008). The role of impairment in the diagnosis of ADHD. *Journal of Attention Disorders*, *11*(5), 529-537.

[18] Dillon, J. E., Blunden, S., Ruzicka, D. L., Guire, K. E., Champine, D., Weatherly, R. A., ... & Chervin, R. D. (2007). DSM-IV diagnoses and obstructive sleep apnea in children before and 1 year after adenotonsillectomy. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(11), 1425-1436.

Pearl, P. L., Weiss, R. E., & Stein, M. A. (2001). Medical mimics: Medical and neurological conditions simulating ADHD. *Annals of the New York Academy of Sciences*, *931*(1), 97-112.

[19] Cortese, S., Solmi, M., Michelini, G., Bellato, A., Blanner, C., Canozzi, A., ... & Correll, C. U. (2023). Candidate diagnostic biomarkers for neurodevelopmental disorders in children and adolescents: A systematic review. *World Psychiatry*, *22*(1), 129-149.

Faraone, S. V., Bonvicini, C., & Scassellati, C. (2014). Biomarkers in the diagnosis of ADHD–promising directions. *Current Psychiatry Reports*, *16*, 1-20.

Thome, J., Ehlis, A. C., Fallgatter, A. J., Krauel, K., Lange, K. W., Riederer, P., ... & Gerlach, M. (2012). Biomarkers for attention-deficit/hyperactivity disorder (ADHD). A consensus report of the WFSBP task force on biological markers and the World Federation of ADHD. *The World Journal of Biological Psychiatry*, *13*(5), 379-400.

Scassellati, C., Bonvicini, C., Faraone, S. V., & Gennarelli, M. (2012). Biomarkers and attention-deficit/hyperactivity disorder: A systematic review and meta-analyses. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(10), 1003-1019.

impairments caused by those symptoms.[20] Although questionnaires and neuropsychological tests are sometimes used in clinical practice to rule in or rule out a diagnosis of ADHD, they have not been cleared for such use by the FDA; nor are they recommended for that purpose in professional guidelines or expert reviews.[21] Thus, at present, the diagnosis of ADHD requires a detailed clinical interview. The interview is the "gold standard" for diagnosing ADHD.[22] Diagnosticians ask about each ADHD symptom, the age at onset, and resultant functional impairment using an accepted standard. This interview establishes that symptoms are more extreme, persistent, and impairing than expected for the patient's developmental level and that they occur in multiple settings.

27. While children can provide useful information for the diagnostician, especially about internal feelings such as anxiety and depression, parents remain the main source of information.[23] Parents can report on symptoms during school recesses and vacations when teacher reports are not available. Although parent reports show good concurrent and predictive validity, information from other informants (e.g., teachers), when available, is valuable for

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[20] American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*. American Psychiatric Publishing.

[21] Pliszka, S., & AACAP Work Group on Quality Issues. (2007). Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(7), 894-921.

Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. (2011). ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, *128*(5), 1007-1022.

Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., ... & Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*, *128*, 789-818.

[22] Pliszka, S., & AACAP Work Group on Quality Issues. (2007). Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(7), 894-921.

Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. (2011). ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, *128*(5), 1007-1022.

[23] Klimkeit, E., Graham, C., Lee, P., Morling, M., Russo, D., & Tonge, B. (2006). Children should be seen and heard: Self-report of feelings and behaviors in primary-school-age children with ADHD. *Journal of Attention Disorders*, *10*(2), 181-191.

documenting ADHD in other settings, for predicting prognosis, and for increasing the confidence of diagnoses.[24] Reports from teachers have been used to document biases in parental reports. For example, when the efficacy of non-pharmacologic treatments has been assessed in systematic reviews that include meta-analyses, some studies have found significant efficacy for parent-reported outcomes but not teacher-reported outcomes.[25] This discrepancy occurs because parents, being involved in the treatment, are not blinded to treatment group, whereas teachers are blinded to treatment group.

28. Diagnosticians also inquire about other medical conditions associated with ADHD symptoms (e.g., seizure disorders, sleep disorders, hyperthyroidism, physical or sexual

[24] Biederman, J., Keenan, K., & Faraone, S. V. (1990). Parent-based diagnosis of attention deficit disorder predicts a diagnosis based on teacher report. *Journal of the American Academy of Child & Adolescent Psychiatry*, *29*(5), 698-701.

Biederman, J., Faraone, S. V., Monuteaux, M. C., & Grossbard, J. R. (2004). How informative are parent reports of attention-deficit/hyperactivity disorder symptoms for assessing outcome in clinical trials of long-acting treatments? A pooled analysis of parents' and teachers' reports. *Pediatrics*, *113*(6), 1667-1671.

Sayal, K., & Goodman, R. (2009). Do parental reports of child hyperkinetic disorder symptoms at school predict teacher ratings?. *European Child & Adolescent Psychiatry*, *18*, 336-344.

de Nijs, P. F., Ferdinand, R. F., de Bruin, E. I., Dekker, M. C., van Duijn, C. M., & Verhulst, D. C. (2004). Attention-deficit/hyperactivity disorder (ADHD): Parents' judgment about school, teachers' judgment about home. *European Child & Adolescent Psychiatry*, *13*, 315-320.

Valo, S., & Tannock, R. (2010). Diagnostic instability of DSM-IV ADHD subtypes: Effects of informant source, instrumentation, and methods for combining symptom reports. *Journal of Clinical Child & Adolescent Psychology*, *39*(6), 749-760.

[25] Sonuga-Barke, E. J., Brandeis, D., Cortese, S., Daley, D., Ferrin, M., Holtmann, M., ... & European ADHD Guidelines Group. (2013). Nonpharmacological interventions for ADHD: Systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *American Journal of Psychiatry*, *170*(3), 275-289.

Cortese, S., Faraone, S. V., Bernardi, S., Wang, S., & Blanco, C. (2016). Gender differences in adult attention-deficit/hyperactivity disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *The Journal of Clinical Psychiatry*, *77*(4), 7626.

Cortese, S., Ferrin, M., Brandeis, D., Buitelaar, J., Daley, D., Dittmann, R. W., ... & European ADHD Guidelines Group. (2015). Cognitive training for attention-deficit/hyperactivity disorder: Meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*(3), 164-174.

abuse, and sensory impairments).[26] Such inquiry is essential because these conditions can mimic ADHD.[27]

**C. Prevalence**

29. True prevalence is estimated by studies that interview parents and/or patients in a defined population to determine if they meet DSM or ICD[28] criteria for having or ever having had ADHD regardless of whether they had been diagnosed with that disorder by a healthcare provider. Some children will not have been diagnosed by a healthcare provider because parents did not realize their child had a disorder that should be brought to the attention of a pediatrician. In other cases, a child may have been misdiagnosed by a provider who was not sufficiently trained or who had been influenced by extraneous factors, such as parental pressures. Diagnosed prevalence refers to the prevalence with which the disorder has been diagnosed by healthcare providers in the community, whether or not criteria for ADHD are satisfied. Diagnosed prevalence is influenced by many factors that are irrelevant to the true prevalence of a disorder such as ADHD and therefore cannot be used to assert that there have or have not been changes in the true prevalence of the disorder over time. For example, one study by Fulton et al. (2009) showed that diagnosed prevalence was associated with the number, age, and type of physicians within a state, particularly pediatricians.[29]

[26] Feldman, H. M., & Reiff, M. I. (2014). Attention deficit-hyperactivity disorder in children and adolescents. *New England Journal of Medicine*, *370*(9), 838-846.

[27] Pearl, P. L., Weiss, R. E., & Stein, M. A. (2001). Medical mimics: Medical and neurological conditions simulating ADHD. *Annals of the New York Academy of Sciences*, *931*(1), 97-112.

[28] Some studies use diagnostic criteria from the International Classification of Diseases (ICD) which are very similar to the DSM criteria.

[29] Fulton, B. D., Scheffler, R. M., Hinshaw, S. P., Levine, P., Stone, S., Brown, T. T., & Modrek, S. (2009). National variation of ADHD diagnostic prevalence and medication use: Health care providers and education policies. *Psychiatric Services*, *60*(8), 1075-1083.

30. A 2007 meta-analysis by Polanczyk et al. estimated the true prevalence of ADHD in children and adolescents to be 5.3% (95% CI: 5.01-5.56).[30] Based on longitudinal studies of clinical samples, ADHD persists into adulthood in more than half of cases.[31] In adults, Simon et al. (2009) found a pooled prevalence of 2.5% (95% CI: 2.1-3.1) based on a meta-analysis of six studies.[32] Studies in older adults found true prevalence rates in the same range.[33]

31. Polanczyk et al. (2007)'s meta-analysis did not find a change in true prevalence over time when considering all the studies or when considering separate geographic locations, meaning that there has not been an increase in the true prevalence of ADHD during the last three decades.[34] The data from Polanczyk's second study are displayed below. The solid line plots the regression predicting true prevalence from year of study. The fact that it is flat indicates that the true prevalence of ADHD has not changed over time. The dotted lines give the 95% confidence intervals for the regression line. Because they are so close together, we can have high confidence in these results. Within time periods, there is variability between studies that is not

[30] Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*(6), 942-948.

[31] Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159-165.

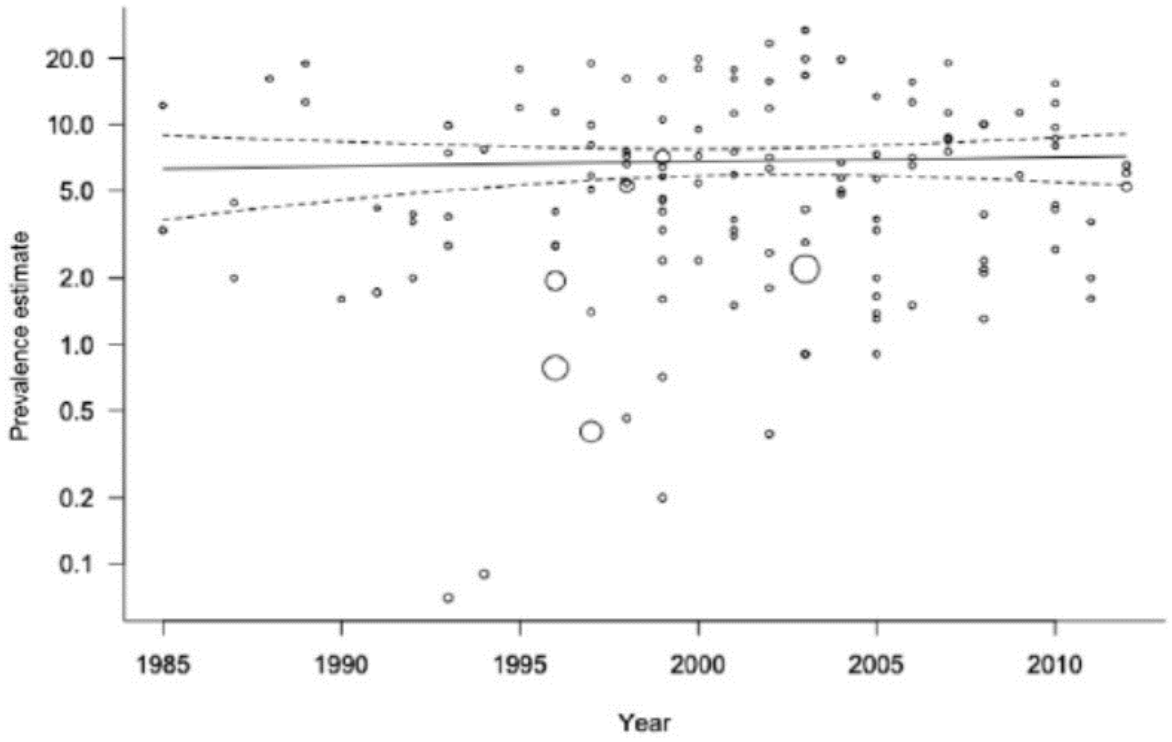
[32] Simon, V., Czobor, P., Bálint, S., Mészáros, A., & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. *The British Journal of Psychiatry*, *194*(3), 204-211.

[33] Michielsen, M., Semeijn, E., Comijs, H. C., van de Ven, P., Beekman, A. T., Deeg, D. J., & Kooij, J. S. (2012). Prevalence of attention-deficit hyperactivity disorder in older adults in The Netherlands. *The British Journal of Psychiatry*, *201*(4), 298-305

Guldberg-Kjär, T., & Johansson, B. (2009). Old people reporting childhood AD/HD symptoms: Retrospectively self-rated AD/HD symptoms in a population-based Swedish sample aged 65-80. *Nordic Journal of Psychiatry*, *63*(5), 375-382.

[34] Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *International Journal of Epidemiology*, *43*(2), 434-442.

due to geographic region but is explained by other methodologic features.




32. Studies similar to the Polanczyk et al. (2007) meta-analysis have also found that ADHD's true prevalence does not differ significantly among countries in Europe, Asia, Africa, Australia, and the Americas, even though acetaminophen use during pregnancy varies widely.[35] Data on acetaminophen usage have shown that acetaminophen use during pregnancy has varied across geographic regions.[36] This difference in variability across geographic regions, which is seen for acetaminophen use during pregnancy, but not for ADHD, undermines the theory that acetaminophen use during pregnancy is causing ADHD.

[35] Id.

Willcutt, E. G. (2012). The prevalence of DSM-IV attention-deficit/hyperactivity disorder: A meta-analytic review. *Neurotherapeutics*, *9*(3), 490-499.

[36] Zafieri A, Mitchell R, Hay D, Folwer P, Over-the-counter analgesics during pregnancy: A comprehensive review of global prevalence and offspring safety. *Human Reproduction Update*, 27(1), 67-95.

33. Plaintiffs' experts do not acknowledge the data from Polanczyk et al. (2014) showing the stability of ADHD's true prevalence over time. Dr. Hollander, for example, cites the study for a different proposition but also contends that rates of ADHD have been increasing.[37] Dr. Baccarelli likewise opines that diagnosed prevalence has increased and states that "[m]ultiple researchers have suggested that in utero acetaminophen use might explain the marked increase in ASD and ADHD rates observed in recent years."[38] These statements confuse increases in the diagnosed prevalence with increases in the true prevalence of ADHD.

34. By contrast to true prevalence, the diagnosed prevalence of ADHD has increased over time. This is due to many factors having nothing to do with acetaminophen use in the population. Over the past few generations, public awareness of mental health and neurodevelopmental disorders has increased substantially in the United States and many other countries.[39] As a result, a higher percentage of parents have their children evaluated for conditions such as ADHD, leading to the diagnosis of a large number of cases that would previously not have been identified.[40] In other words, it is highly likely that prior to the past decade, ADHD was substantially underdiagnosed.

35. Other trends can also explain increased diagnosed prevalence of ADHD. For example, Fulton et al. (2015) examined the impact on the diagnosed prevalence of ADHD caused by the accountability reforms initiated by the No Child Left Behind (NCLB) Act.[41] They

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[37] Eric Hollander, M.D., DFAPA, FACNP Amended Report, dated June 23, 2023, at 39.

[38] Andrea Baccarelli, M.D., Ph.D., MPH Amended Report, dated June 23, 2023, at 4.

[39] Johnson, A. L. (2021). Changes in mental health and treatment, 1997-2017. *Journal of Health and Social Behavior*, *62*(1), 53-68.

[40] Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: An updated systematic review and meta-regression analysis. *International Journal of Epidemiology*, *43*(2), 434-442.

[41] Fulton, B. D., Scheffler, R. M., & Hinshaw, S. P. (2015). State variation in increased ADHD prevalence: Links to NCLB school accountability and state medication laws. *Psychiatric Services*, *66*(10), 1074-1082.

found that NCLB-initiated reforms that sought to make schools more accountable for student performance were associated with more ADHD diagnoses among low-income children, consistent with increased academic pressures from NCLB for this subgroup. Similar findings were reported by Schneider and Eisenberg.[42] Relatedly, under American disabilities law, students diagnosed with ADHD are entitled to certain academic accommodations, which further incentivizes testing that may not have been performed in previous generations.

## IV.

## ADHD PATHOPHYSIOLOGY

36. There is no single brain lesion associated with ADHD, and there is no brain measure that reliably differentiates people with ADHD from people without ADHD.[43] There is also no definitive pathophysiology (i.e., disordered physiological processes associated with disease), as I have documented with colleagues in review articles.[44] Other specialists in ADHD agree with this conclusion.[45] A problem that further complicates conclusions about the

[42] Schneider, H., & Eisenberg, D. (2006). Who receives a diagnosis of attention-deficit/hyperactivity disorder in the United States elementary school population? *Pediatrics*, *117*(4), e601-e609.

[43] Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., ... & Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*, *128*, 789-818.

[44] Zhang-James, Y., Chen, Q., Kuja-Halkola, R., Lichtenstein, P., Larsson, H., & Faraone, S. V. (2020). Machine-Learning prediction of comorbid substance use disorders in ADHD youth using Swedish registry data. *Journal of Child Psychology and Psychiatry*, *61*(12), 1370-1379.

Scassellati, C., Bonvicini, C., Faraone, S. V., & Gennarelli, M. (2012). Biomarkers and attention-deficit/hyperactivity disorder: A systematic review and meta-analyses. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(10), 1003-1019.

Faraone, S. V., Bonvicini, C., & Scassellati, C. (2014). Biomarkers in the diagnosis of ADHD–promising directions. *Current Psychiatry Reports*, *16*, 1-20.

Buitelaar, J., Bölte, S., Brandeis, D., Caye, A., Christmann, N., Cortese, S., ... & Banaschewski, T. (2022). Toward precision medicine in ADHD. *Frontiers in Behavioral Neuroscience*, *16*, 900981.

[45] Thome, J., Ehlis, A. C., Fallgatter, A. J., Krauel, K., Lange, K. W., Riederer, P., ... & Gerlach, M. (2012). Biomarkers for attention-deficit/hyperactivity disorder (ADHD). A consensus report of the WFSBP task force on biological markers and the World Federation of ADHD. *The World Journal of Biological Psychiatry*, *13*(5), 379-400.

pathophysiology of ADHD is the fact that stress and other secondary consequences associated with ADHD can cause changes to the brain. In other words, it is hard to know whether changes to the brain seen with ADHD are a cause of the condition or a result of it.

37. Many hypotheses on the pathophysiology of ADHD have been proposed, but none has been demonstrated to be correct. It is known that many small changes in the brain have been associated with ADHD, but these small changes do not occur in all or even in a large majority of people with ADHD.[46]

38. The two main sources of data about the pathophysiology of ADHD derive from neuropsychopharmacology and neuroimaging. These findings are not used to diagnose the

Pulini, A. A., Kerr, W. T., Loo, S. K., & Lenartowicz, A. (2019). Classification accuracy of neuroimaging biomarkers in attention-deficit/hyperactivity disorder: Effects of sample size and circular analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*(2), 108-120.

Cortese, S., Solmi, M., Michelini, G., Bellato, A., Blanner, C., Canozzi, A., ... & Correll, C. U. (2023). Candidate diagnostic biomarkers for neurodevelopmental disorders in children and adolescents: A systematic review. *World Psychiatry*, *22*(1), 129-149.

[46] Wolfers, T., Beckmann, C. F., Hoogman, M., Buitelaar, J. K., Franke, B., & Marquand, A. F. (2020). Individual differences v. the average patient: Mapping the heterogeneity in ADHD using normative models. *Psychological Medicine*, *50*(2), 314-323.

Mostert, J. C., Onnink, A. M. H., Klein, M., Dammers, J., Harneit, A., Schulten, T., ... & Hoogman, M. (2015). Cognitive heterogeneity in adult attention deficit/hyperactivity disorder: A systematic analysis of neuropsychological measurements. *European Neuropsychopharmacology*, *25*(11), 2062-2074.

Fair, D. A., Bathula, D., Nikolas, M. A., & Nigg, J. T. (2012). Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD. *Proceedings of the National Academy of Sciences*, *109*(17), 6769-6774.

Brookes, K. J., Xu, X., Anney, R., Franke, B., Zhou, K., Chen, W., ... & Asherson, P. (2008). Association of ADHD with genetic variants in the 5′-region of the dopamine transporter gene: Evidence for allelic heterogeneity. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *147*(8), 1519-1523.

van't Ent, D., Lehn, H., Derks, E. M., Hudziak, J. J., Van Strien, N. M., Veltman, D. J., ... & Boomsma, D. I. (2007). A structural MRI study in monozygotic twins concordant or discordant for attention/hyperactivity problems: Evidence for genetic and environmental heterogeneity in the developing brain. *Neuroimage*, *35*(3), 1004-1020.

disorder.[47] However, they provide indirect evidence of the potential mechanisms by which ADHD might develop.

**A. Neuropsychopharmacology**

39. Neuropsychopharmacology is the scientific study of the action of drugs on the central nervous system and their consequent effects on the mind and behavior. The types of drugs that treat the symptoms of ADHD have been used to infer which brain circuits are involved in the disorder.[48]

40. The two main classes of drugs used to treat ADHD are stimulants and non-stimulants. Stimulant drugs primarily increase the activity of dopamine, a chemical messenger in the brain. The two types of non-stimulant drugs are norepinephrine transporter inhibitors and alpha-2 agonists. These drugs primarily increase the transmission of norepinephrine in the brain.

41. Based upon the mechanism of action of these drugs, researchers have theorized that people with ADHD may have abnormalities in the molecules and brain networks responsible for the transmission of dopamine and norepinephrine. The strongest evidence supporting these theories is found in studies of the dopamine transporter, which is the target of stimulant medications. Studies using single-photon emission computed tomography and positron emission tomography (PET) have found that adults with ADHD have more dopamine transporters in the brain than adults who have not been diagnosed with ADHD, although some data suggest this finding could be secondary to treatment with stimulant medications.[49] Because the dopamine

[47] Zhang-James, Y., Razavi, A. S., Hoogman, M., Franke, B., & Faraone, S. V. (2023). Machine learning and MRI-based diagnostic models for ADHD: Are we there yet?. *Journal of Attention Disorders*, *27*(4), 335-353.

[48] Faraone, S. V. (2018). The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neuroscience & Biobehavioral Reviews*, *87*, 255-270.

[49] Faraone, S. V., Spencer, T. J., Madras, B. K., Zhang-James, Y., & Biederman, J. (2014). Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: A meta-analysis. *Molecular Psychiatry*, *19*(8), 880-889.

transporter clears dopamine from the space between neurons, having too many transporters reduces the ability of neurons to communicate with one another using dopamine. Further evidence for the role of dopamine in ADHD comes from the Genome Wide Association Study (GWAS) of ADHD.[50] A GWAS assays DNA from people with and without ADHD across the entire genome. In the ADHD GWAS results, we reported that the genetic risk for ADHD was associated, in part, with genomic loci (that is, specific genes or segments of DNA) regulating neurons that communicate with dopamine.[51]

42. Norepinephrine has also been implicated in the etiology of ADHD because two types of drugs that target the brain's norepinephrine system are useful in treating ADHD.[52] One type of drug is the norepinephrine transporter reuptake inhibitor, which has effects on norepinephrine in the synapse that are similar to the effects of the dopamine transporter on

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Krause, K. H., Dresel, S. H., Krause, J., Kung, H. F., & Tatsch, K. (2000). Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: Effects of methylphenidate as measured by single photon emission computed tomography. *Neuroscience Letters*, *285*(2), 107-110.

Krause, K. H., Dresel, S. H., Krause, J., la Fougere, C., & Ackenheil, M. (2003). The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. *Neuroscience & Biobehavioral Reviews*, *27*(7), 605-613.

Larisch, R., Sitte, W., Antke, C., Nikolaus, S., Franz, M., Tress, W., & Müller, H. W. (2006). Striatal dopamine transporter density in drug naive patients with attention-deficit/hyperactivity disorder. *Nuclear Medicine Communications*, *27*(3), 267-270.

Spencer, T. J., Biederman, J., Madras, B. K., Dougherty, D. D., Bonab, A. A., Livni, E., ... & Fischman, A. J. (2007). Further evidence of dopamine transporter dysregulation in ADHD: A controlled PET imaging study using altropane. *Biological Psychiatry*, *62*(9), 1059-1061.

Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., & Balottin, U. (2012). Striatal dopamine transporter alterations in ADHD: Pathophysiology or adaptation to psychostimulants? A meta-analysis. *American Journal of Psychiatry*, *169*(3), 264-272.

[50] Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., ... & Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*, *55*(2), 198-208.

[51] Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., ... & Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*, *55*(2), 198-208.

[52] Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., ... & Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, *1*, 15020.

dopamine in the synapse. The drugs used are atomoxetine and extended-release viloxazine. The second type of drug is the alpha-2 agonist, which activates alpha-2 receptors. The alpha-2 drugs used are extended-release versions of clonidine and guanfacine.

43. Although the efficacy of these treatments provides clues to the pathophysiology of ADHD in children and adults diagnosed years after birth, they do not reveal the underlying mechanisms for how or why ADHD develops.

**B. Neuroimaging**

44. Neuroimaging studies have not described a definitive pathophysiology of ADHD. The differences in brain structure and function between people with and without ADHD are so small that they would not be noticed by a radiologist examining the images of a few patients with ADHD.[53] They are also heterogeneous, which means that the types of brain structure differences seen in patients with ADHD will vary from patient to patient.[54] This heterogeneity is consistent with the heterogeneity of cognitive changes associated with ADHD.[55] Because the brain differences associated with ADHD are small and because there is no "neuroimaging signature"

[53] Here I refer to the large majority of patients with ADHD. Those who develop ADHD secondary to traumatic brain injury will have clinically significant results.

[54] Wolfers, T., Beckmann, C. F., Hoogman, M., Buitelaar, J. K., Franke, B., & Marquand, A. F. (2020). Individual differences v. the average patient: Mapping the heterogeneity in ADHD using normative models. *Psychological Medicine*, *50*(2), 314-323.

[55] Mostert, J. C., Onnink, A. M. H., Klein, M., Dammers, J., Harneit, A., Schulten, T., ... & Hoogman, M. (2015). Cognitive heterogeneity in adult attention deficit/hyperactivity disorder: A systematic analysis of neuropsychological measurements. *European Neuropsychopharmacology*, *25*(11), 2062-2074.

Fair, D. A., Bathula, D., Nikolas, M. A., & Nigg, J. T. (2012). Distinct neuropsychological subgroups in typically developing youth inform heterogeneity in children with ADHD. *Proceedings of the National Academy of Sciences*, *109*(17), 6769-6774.

that is common to all cases of ADHD,[56] neuroimaging cannot be used to diagnose ADHD accurately in an individual patient.[57]

45. Another limitation is the significant variability in neuroimaging study results. Because there is considerable heterogeneity in the ADHD population in terms of age, gender, comorbid conditions, and medication status, neuroimaging results are highly variable across studies. Numerous studies have reported differences in brain structure and function in individuals with ADHD compared to controls. They show a wide range of small brain changes associated with ADHD rather than a single, consistent pattern,[58] and the specific regions implicated vary widely across studies. For instance, some studies have reported reductions in the size of the prefrontal cortex, while others have found abnormalities in the basal ganglia or cerebellum.[59] This lack of consistency makes it challenging to draw definitive conclusions. In fact, when my colleagues and I pooled data across many small studies, we found that most prior findings could not be confirmed.[60] Moreover, the pooled study found only a few small differences for children and none for adolescents or adults.

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[56] Wolfers, T., Beckmann, C. F., Hoogman, M., Buitelaar, J. K., Franke, B., & Marquand, A. F. (2020). Individual differences v. the average patient: Mapping the heterogeneity in ADHD using normative models. *Psychological Medicine*, *50*(2), 314-323.

[57] Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., ... & Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*, *128*, 789-818.

[58] Wolfers, T., Beckmann, C. F., Hoogman, M., Buitelaar, J. K., Franke, B., & Marquand, A. F. (2020). Individual differences v. the average patient: Mapping the heterogeneity in ADHD using normative models. *Psychological Medicine*, *50*(2), 314-323.

[59] Arnsten, A. F. (2009). Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: An important role for prefrontal cortex dysfunction. *CNS Drugs*, *23*, 33-41.

Berquin, P. C., Giedd, J. N., Jacobsen, L. K., Hamburger, S. D., Krain, A. L., Rapoport, J. L., & Castellanos, F. X. (1998). Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology*, *50*(4), 1087-1093.

[60] Hoogman, M., Van Rooij, D., Klein, M., Boedhoe, P., Ilioska, I., Li, T., ... & Franke, B. (2022). Consortium neuroscience of attention deficit/hyperactivity disorder and autism spectrum disorder: The ENIGMA adventure. *Human Brain Mapping*, *43*(1), 37-55.

46. The complexity of ADHD also contributes to the inconclusiveness of neuroimaging studies. ADHD is not a homogeneous disorder; it presents with different sets of diagnostic symptoms and severity levels. Moreover, the fact that ADHD often co-occurs with other psychiatric disorders, such as depression and anxiety, further complicates the interpretation of neuroimaging studies because researchers do not always document all comorbidities, making it difficult to tease apart the brain differences that account for each disorder and their overlap.

47. Given these limitations, the best data available on neuroimaging studies for ADHD come from meta-analyses, which combine many small studies with the goal of increasing statistical power and identifying true associations. These findings provide clues that have been useful for devising hypotheses and theories on the pathophysiology of ADHD. They do not constitute a definitive pathophysiology of the disorder and are not useful for making diagnoses of ADHD.

48. Meta-analyses of functional MRI studies show that people with ADHD do not fully activate the brain networks that regulate attention when faced with tasks requiring attention.[61] These networks support goal-directed processes and are needed for orientation to salient and important stimuli in the environment. ADHD is also associated with hyperactivation in brain systems regulating vision and movement.[62] Other meta-analyses of such studies report

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Hoogman, M., Muetzel, R., Guimaraes, J. P., Shumskaya, E., Mennes, M., Zwiers, M. P., ... & Franke, B. (2019). Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples. *American Journal of Psychiatry*, *176*(7), 531-542.

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S., ... & Franke, B. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *The Lancet Psychiatry*, *4*(4), 310-319.

[61] Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*, *169*(10), 1038-1055.

[62] Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., & Castellanos, F. X. (2012). Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *American Journal of Psychiatry*, *169*(10), 1038-1055.

underactivation in the inferior frontal cortex and insula in ADHD.[63] Meta-analyses also report underactivation in right or bilateral dorsolateral prefrontal cortex.[64]

49. Resting-state MRI allows researchers to examine how the brain changes when it moves from a state of rest (such as daydreaming) to a state of activation (such as a goal-directed activity). A leading hypothesis is that the network that is active during daydreaming interferes with the network required for goal-directed activities among people with ADHD. Put simply, the ADHD brain tends to go "offline" when it should be "online" and vice-versa. However, the evidence supporting this hypothesis is mixed. Two meta-analyses support the hypothesis, but they were limited because they did not assess activities in the entire brain.[65] A whole-brain meta-analysis failed to support the hypothesis.[66]

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[63] Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., & Rubia, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*, *70*(2), 185-198.

Rubia, K., Norman, L., Lukito, S., Alegria, A., & Wulff, M. Neuroimaging of ADHD: From matter over mind to mind over matter. *Frontiers in Human Neuroscience*.

Lukito, S., Norman, L., Carlisi, C., Radua, J., Hart, H., Simonoff, E., & Rubia, K. (2020). Comparative meta-analyses of brain structural and functional abnormalities during cognitive control in attention-deficit/hyperactivity disorder and autism spectrum disorder. *Psychological Medicine*, *50*(6), 894-919.

Samea, F., Soluki, S., Nejati, V., Zarei, M., Cortese, S., Eickhoff, S. B., ... & Eickhoff, C. R. (2019). Brain alterations in children/adolescents with ADHD revisited: A neuroimaging meta-analysis of 96 structural and functional studies. *Neuroscience & Biobehavioral Reviews*, *100*, 1-8.

[64] Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., & Rubia, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: Exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry*, *70*(2), 185-198.

McCarthy, H., Skokauskas, N., & Frodl, T. (2014). Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: A meta-analysis. *Psychological Medicine*, *44*(4), 869-880.

[65] Gao, Y., Shuai, D., Bu, X., Hu, X., Tang, S., Zhang, L., ... & Huang, X. (2019). Impairments of large-scale functional networks in attention-deficit/hyperactivity disorder: A meta-analysis of resting-state functional connectivity. *Psychological Medicine*, *49*(15), 2475-2485.

Sutcubasi, B., Metin, B., Kurban, M. K., Metin, Z. E., Beser, B., & Sonuga-Barke, E. (2020). Resting-state network dysconnectivity in ADHD: A system-neuroscience-based meta-analysis. *The World Journal of Biological Psychiatry*, *21*(9), 662-672.

[66] Cortese, S., Aoki, Y. Y., Itahashi, T., Castellanos, F. X., & Eickhoff, S. B. (2021). Systematic review and meta-analysis: Resting-state functional magnetic resonance imaging studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*(1), 61-75.

50. A meta-analysis of structural MRI studies of children reported that ADHD is associated with small reductions in volumes of subcortical regions of the brain and the thickness of some cortical areas; these reductions are so small that they can only be detected when comparing large groups of ADHD subjects with non-ADHD controls.[67] These brain differences were documented for ADHD in children, but no structural brain differences were found in the meta-analyses of adolescent or adult data. In addition to these differences in brain volumes, other studies have documented widespread alterations in the interconnections among brain regions.[68] This means that in ADHD, not only are there small, heterogenous changes in the size of brain structures, but there are also small and heterogeneous changes in how these structures connect to one another.

51. Changes across age in the brains of people with ADHD are of much interest given that longitudinal studies of youth with ADHD show that one-third will remit their symptoms in young adulthood.[69] Consistent with this finding, some brain volumetric alterations observed in childhood normalize with age.[70] ADHD is also associated with delayed maturation of the cerebral

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[67] Hoogman, M., Van Rooij, D., Klein, M., Boedhoe, P., Ilioska, I., Li, T., ... & Franke, B. (2022). Consortium neuroscience of attention deficit/hyperactivity disorder and autism spectrum disorder: The ENIGMA adventure. *Human Brain Mapping*, *43*(1), 37-55.

Hoogman, M., Muetzel, R., Guimaraes, J. P., Shumskaya, E., Mennes, M., Zwiers, M. P., ... & Franke, B. (2019). Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples. *American Journal of Psychiatry*, *176*(7), 531-542.

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S., ... & Franke, B. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *The Lancet Psychiatry*, *4*(4), 310-319.

[68] van Ewijk, H., Heslenfeld, D. J., Zwiers, M. P., Buitelaar, J. K., & Oosterlaan, J. (2012). Diffusion tensor imaging in attention deficit/hyperactivity disorder: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *36*(4), 1093-1106.

[69] Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159-165.

[70] Hoogman, M., Van Rooij, D., Klein, M., Boedhoe, P., Ilioska, I., Li, T., ... & Franke, B. (2022). Consortium neuroscience of attention deficit/hyperactivity disorder and autism spectrum disorder: The ENIGMA adventure. *Human Brain Mapping*, *43*(1), 37-55.

Hoogman, M., Muetzel, R., Guimaraes, J. P., Shumskaya, E., Mennes, M., Zwiers, M. P., ... & Franke, B. (2019). Brain imaging of the cortex in ADHD: A coordinated analysis of large-scale clinical and population-based samples. *American Journal of Psychiatry*, *176*(7), 531-542.

cortex. Shaw et al. (2007) reported that the age of attaining peak cortical thickness was 10.5 years for patients with ADHD and 7.5 years for controls.[71] This delay was most prominent in the prefrontal cortex, which is important for control of executive functioning, attention, and motor planning.[72] Remission of ADHD has been associated with normalization of abnormalities as measured by activation during functional imaging tasks, cortical thinning, and functional and structural brain connectivity.[73]

52. Plaintiff expert Dr. Hollander writes that, "[d]epending on the timing and duration of APAP exposure to the developing brain, if the suspect mechanisms of injury occur, then one would expect a wide variety of diffuse neurologic symptoms/injuries when the brain

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Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S., ... & Franke, B. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *The Lancet Psychiatry*, *4*(4), 310-319.

Frodl, T., & Skokauskas, N. (2012). Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. *Acta Psychiatrica Scandinavica*, *125*(2), 114-126.

[71] Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D. E. E. A., ... & Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences*, *104*(49), 19649-19654.

[72] Id.

[73] Dreisbach, G., Müller, J., Goschke, T., Strobel, A., Schulze, K., Lesch, K. P., & Brocke, B. (2005). Dopamine and cognitive control: The influence of spontaneous eyeblink rate and dopamine gene polymorphisms on perseveration and distractibility. *Behavioral Neuroscience*, *119*(2), 483-90.

Makris, N., Biederman, J., Valera, E. M., Bush, G., Kaiser, J., Kennedy, D. N., ... & Seidman, L. J. (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cerebral Cortex*, *17*(6), 1364-1375.

Clerkin, S. M., Schulz, K. P., Berwid, O. G., Fan, J., Newcorn, J. H., Tang, C. Y., & Halperin, J. M. (2013). Thalamo-cortical activation and connectivity during response preparation in adults with persistent and remitted ADHD. *American Journal of Psychiatry*, *170*(9), 1011-1019.

Mattfeld, A. T., Gabrieli, J. D., Biederman, J., Spencer, T., Brown, A., Kotte, A., ... & Whitfield-Gabrieli, S. (2014). Brain differences between persistent and remitted attention deficit hyperactivity disorder. *Brain*, *137*(9), 2423-2428.

Francx, W., Zwiers, M. P., Mennes, M., Oosterlaan, J., Heslenfeld, D., Hoekstra, P. J., ... & Buitelaar, J. K. (2015). White matter microstructure and developmental improvement of hyperactive/impulsive symptoms in attention-deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, *56*(12), 1289-1297.

develops."[74] But if that were the case, acetaminophen exposure would be expected to cause many neurologic and psychiatric disorders. I know of no data supporting that hypothesis.

## V.

## ADHD ETIOLOGY

53. Studies demonstrate that the causes of ADHD are predominantly genetic. Parents and siblings of children with ADHD have a five- to ten-fold increased risk of having ADHD compared with the general population, and twin studies conclude that the heritability of ADHD is 75%.[75] This substantial heritability calculation does not account for de novo mutations that occur in the child but not their parents.

54. Studies also show that genetic causes are shared between ADHD and a wide range of other neurodevelopmental and psychopathological traits and disorders.[76] Research into the genetic basis for ADHD is ongoing, and the discovery of new variants is expected to continue.

55. The human genome can be illustrated by a very long series of beads on a string representing genes that are inherited from both parents. Each bead can have one of four colors. If the bead (gene) is very important for survival, it is the same color for all or nearly all people. If it is not, then the colors will vary among people. The different colors represent DNA variants, and the goal of a GWAS is to see if some variants are associated with a disorder.

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[74] Hollander Amended Rep. at 4, 86.

[75] Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562-575.

[76] Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562-575.

Smoller, J. W., Andreassen, O. A., Edenberg, H. J., Faraone, S. V., Glatt, S. J., & Kendler, K. S. (2019). Psychiatric genetics and the structure of psychopathology. *Molecular Psychiatry*, *24*(3), 409-420.

Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., ... & Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*, *55*(2), 198-208.

56. I was co-leader of an international collaboration that studied the DNA of 38,691 people with ADHD and 186,843 without ADHD using GWAS.[77]

57. An important conclusion from this work is that many DNA variants, each having small effects, contribute to the etiology of ADHD. Because many of the variants implicated in ADHD involve genes that are expressed in the brain rather than other parts of the body, my co-authors and I concluded that the genomic data provided further evidence that ADHD is a brain disorder that is strongly influenced by genetics.

58. The study team estimated that there are about 7,000 DNA variants involved in the etiology of the disorder. Most cases of ADHD are caused by relatively common genetic variants that occur in 5% or more of the population, but studies have documented the existence of rare variants that also cause ADHD,[78] and that occur in 1% of the population or less.

59. In contrast to the many identified genetic causes of ADHD, there are only two environmental events that are strongly supported as causes of ADHD: traumatic brain injury and severe, early deprivation in orphanages.[79] Many potential environmental exposures have been

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[77] Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., ... & Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*, *55*(2), 198-208.

[78] Elia, J., Gai, X., Xie, H. M., Perin, J. C., Geiger, E., Glessner, J. T., ... & White, P. S. (2010). Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. *Molecular Psychiatry*, *15*(6), 637-646.

Williams, N. M., Zaharieva, I., Martin, A., Langley, K., Mantripragada, K., Fossdal, R., ... & Thapar, A. (2010). Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: A genome-wide analysis. *The Lancet*, *376*(9750), 1401-1408.

Williams, N. M., Franke, B., Mick, E., Anney, R. J., Freitag, C. M., Gill, M., ... & Faraone, S. V. (2012). Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: The role of rare variants and duplications at 15q13. 3. *American Journal of Psychiatry*, *169*(2), 195-204.

Satterstrom, F. K., Walters, R. K., Singh, T., Wigdor, E. M., Lescai, F., Demontis, D., ... & Daly, M. J. (2019). Autism spectrum disorder and attention deficit hyperactivity disorder have a similar burden of rare protein-truncating variants. *Nature Neuroscience*, *22*(12), 1961-1965.

[79] Adeyemo, B. O., Biederman, J., Zafonte, R., Kagan, E., Spencer, T. J., Uchida, M., ... & Faraone, S. V. (2014). Mild traumatic brain injury and ADHD: A systematic review of the literature and meta-analysis. *Journal of Attention Disorders*, *18*(7), 576-584.

studied using methods of observational epidemiology but, due to limitations inherent in those studies, none of the environmental exposures found to have a statistical association with ADHD has been determined to be causal.

60. One limitation in studies of environmental exposures is the absence of genetic testing. In the absence of genome wide testing, sibling control studies can account for potential contribution of genetics to neurodevelopmental outcomes. When certain environmental risk factors reported to have been associated with ADHD were subsequently evaluated using sibling control study designs, the associations weakened or were completely eliminated. Indeed, large cohorts from country-wide databases (e.g., Sweden, Denmark, Norway) have identified several other risk factors associated with ADHD that disappeared when sub-analyses or follow-up studies used sibling controls.[80] Sibling control studies show why epidemiological studies

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Stevens, S. E., Sonuga-Barke, E. J., Kreppner, J. M., Beckett, C., Castle, J., Colvert, E., ... & Rutter, M. (2008). Inattention/overactivity following early severe institutional deprivation: Presentation and associations in early adolescence. *Journal of Abnormal Child Psychology*, *36*, 385-398.

[80] Maternal BMI: Chen, M. H., Pan, T. L., Wang, P. W., Hsu, J. W., Huang, K. L., Su, T. P., ... & Bai, Y. M. (2019). Prenatal exposure to acetaminophen and the risk of attention-deficit/hyperactivity disorder: A nationwide study in Taiwan. *The Journal of Clinical Psychiatry*, *80*(5), 15264.

Maternal Smoking: Skoglund, C., Chen, Q., D'Onofrio, B. M., Lichtenstein, P., & Larsson, H. (2014). Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. *Journal of Child Psychology and Psychiatry*, *55*(1), 61-68.

C-sections: Curran, E. A., Khashan, A. S., Dalman, C., Kenny, L. C., Cryan, J. F., Dinan, T. G., & Kearney, P. M. (2016). Obstetric mode of delivery and attention-deficit/hyperactivity disorder: A sibling-matched study. *International Journal of Epidemiology*, *45*(2), 532-542.

Maternal Smoking: Gustavson, K., Ystrom, E., Stoltenberg, C., Susser, E., Surén, P., Magnus, P., ... & Reichborn-Kjennerud, T. (2017). Smoking in pregnancy and child ADHD. *Pediatrics*, *139*(2), e20162509.

Oxytocin-Induced Labor Induction: Wiggs, K. K., Rickert, M. E., Hernandez-Diaz, S., Bateman, B. T., Almqvist, C., Larsson, H., ... & D'Onofrio, B. M. (2017). A family-based study of the association between labor induction and offspring attention-deficit hyperactivity disorder and low academic achievement. *Behavior Genetics*, *47*, 383-393.

C-sections: Axelsson, P. B., Clausen, T. D., Petersen, A. H., Hageman, I., Pinborg, A., Kessing, L. V., ... & Løkkegaard, E. C. L. (2019). Investigating the effects of cesarean delivery and antibiotic use in early childhood on risk of later attention deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, *60*(2), 151-159.

evaluating whether there is any relationship between ADHD and environmental exposures need to control for genetics and early-life environmental factors shared among siblings to be meaningful. Many such factors, however, have not yet been fully evaluated using this study design, leaving open the question of whether these associations are due to residual confounding.

## VI.

## LITERATURE ADDRESSING THE POTENTIAL ASSOCIATION BETWEEN MATERNAL USE OF ACETAMINOPHEN DURING PREGNANCY AND THE DEVELOPMENT OF ADHD IN OFFSPRING

61. This section identifies and evaluates the published literature addressing whether maternal acetaminophen use during pregnancy causes ADHD in offspring.

### A. What Types of Outcome Data Are Relevant?

62. To evaluate whether in utero acetaminophen exposure is associated with ADHD in offspring, the best approach is to use clinically diagnosed cases of ADHD as the end point. Plaintiffs' experts, by contrast, rely on literature with little relevance to the subject at hand. Dr. Cabrera, for example, discusses acute liver toxicity at great length,[81] and cites literature related to everything from rodent sexual behavior[82] to acute poisoning[83] to cancer.[84] He does not explain, nor am I aware of, how these relate to ADHD.

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Use of ADHD Medication: Lemelin, M., Sheehy, O., Zhao, J. P., & Bérard, A. (2021). Maternal ADHD medication use during pregnancy and the risk of ADHD in children: Importance of genetic predispositions and impact of using a sibling analysis. *European Neuropsychopharmacology*, *44*, 66-78.

Labor Epidural Analgesia: Hegvik, T. A., Klungsøyr, K., Kuja-Halkola, R., Remes, H., Haavik, J., D'Onofrio, B. M., ... & Sariaslan, A. (2023). Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: A cross-national cohort study of 4.5 million individuals and their siblings. *American Journal of Obstetrics and Gynecology*, *228*(2), 233-e1.

[81] E.g., Cabrera Amended Rep. at 8, 20-25, 29-31.

[82] E.g., id. at 106.

[83] E.g., id. at 95.

[84] E.g., id. at 187-188.

63. Plaintiffs' expert Dr. Hollander uses a "transdiagnostic approach" that improperly considers various neurodevelopmental disorders—including ADHD and autism spectrum disorder (ASD)—as if they were a single disorder. He asserts that "when analysing causal associations between a toxic exposure and neurodevelopmental disorders such as ASD and ADHD, it is appropriate to consider comprehensive evidence that examines a variety of neurodevelopmental symptoms."[85] Dr. Hollander also characterizes the distinctions between ASD and ADHD as "artificial" and states that "ASD and ADHD share important neural, genetic, physiological, structural, and psychological traits."[86]

64. The diagnostic criteria for ADHD and ASD have been validated by decades of research, including in DSM field trials.[87] The criteria are very different for each disorder. None of the behavioral diagnostic criteria of one disorder are included as behavioral diagnostic criteria for the other disorder in either the DSM or ICD. These diagnostic criteria have been shown to be clinically useful categories that predict course, outcome, response to treatment, and family history, which are the appropriate bases for validating diagnostic boundaries.[88] I have used the diagnostic criteria to validate the diagnosis of ADHD in my research.[89]

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[85] Hollander Amended Rep. at 2-3.

[86] Id. at 3, 10.

[87] Matte, B., Anselmi, L., Salum, G. A., Kieling, C., Gonçalves, H., Menezes, A., ... & Rohde, L. A. (2015). ADHD in DSM-5: A field trial in a large, representative sample of 18-to 19-year-old adults. *Psychological Medicine*, *45*(2), 361-373.

Regier, D. A., Narrow, W. E., Clarke, D. E., Kraemer, H. C., Kuramoto, S. J., Kuhl, E. A., & Kupfer, D. J. (2013). DSM-5 field trials in the United States and Canada, Part II: Test-retest reliability of selected categorical diagnoses. *American Journal of Psychiatry*, *170*(1), 59-70.

Volkmar, F. R., Klin, A., Siegel, B., Szatmari, P., Lord, C., Campbell, M., ... & Kline, W. (1994). Field trial for autistic disorder in DSM-IV. *The American Journal of Psychiatry*, *151*(9), 1361-1367.

[88] Robins, E., & Guze, S. B. (1970). Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. *American Journal of Psychiatry*, *126*(7), 983-987.

[89] Faraone, S. V. (2005). The scientific foundation for understanding attention-deficit/hyperactivity disorder as a valid psychiatric disorder. *European Child & Adolescent Psychiatry*, *14*(1), 1-10.

65. Despite superficial similarities between ADHD and ASD, there are important differences between these conditions. For example, youth with either condition can have difficulties socializing. But the socialization deficits due to ADHD are very different from the socialization deficits seen in ASD. In ADHD, socialization problems are secondary to the primary symptoms of inattention, impulsivity, and hyperactivity. Children with ADHD interrupt conversations, have trouble waiting their turn in games or activities, and act without thinking about the social consequences. This makes it difficult for them to maintain friendships and can lead to rejection by peers. They may also miss out on subtle social cues due to inattentiveness, which can lead to inappropriate responses in social situations. Their difficulties in concentrating may also make them seem like they are not listening in conversations, which can frustrate their peers and lead to misunderstandings.

66. By contrast, for youth with ASD, social communication deficits are a defining characteristic of the disorder. These deficits are more pervasive and complex than those typically seen in ADHD. Children with ASD have difficulty understanding and responding to social cues, such as body language, facial expressions, and tone of voice, which is due not just to inattentiveness but also to a fundamental difficulty in social understanding and communication. They often struggle with understanding the perspective of others, which can lead to problems in reciprocal social interactions because they cannot understand that others have beliefs, desires, intentions, and perspectives that are different from their own. Unlike the child with ADHD, the child with ASD may not naturally engage in sharing interests or emotions with others. They often have difficulty in initiating and maintaining back-and-forth conversations. Moreover, in stark contrast to youth with ADHD, those with ASD may show little interest in making friends or prefer

to play alone. Their repetitive behaviors and restricted interests further limit their social interactions.

67. These differences between ADHD and ASD patients have been documented in the literature. One review reported that for ADHD patients, social performance deficits were incurred by disruption arising from the ADHD symptoms of inattention and hyperactivity/impulsivity. In other words, the patients' inattentive, intrusive, and impulsive behaviors could unsettle social interaction, but their acquisition capacity for social knowledge was relatively intact.[90] By contrast, ASD patients had a social knowledge/behavior deficit arising from difficulties in social/emotional cue detection, encoding, and interpretation, leading to problems in joining and initiating social interaction.[91] Another review concluded that social cognition deficits were mild or nonexistent for ADHD, but severe for ASD.[92] In short, while both ADHD and ASD affect socialization, the root causes of the social difficulties differ. ADHD-related social problems often stem from issues with impulsivity and inattention, while ASD-related social problems typically involve a more fundamental impairment in social understanding and communication.

68. Other evidence reinforces the distinctness of ASD and ADHD. Although ASD co-occurs with ADHD more than expected by chance alone, the co-occurrence rate is relatively small. Only a quarter of youth with one disorder will also have the other disorder, and the two disorders share only 18% of their genomic variance.[93] In addition, although there are some

[90] Chan, J. K., & Leung, P. W. (2022). Common outcome, different pathways: Social information-processing deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. *World Journal of Psychiatry*, *12*(2), 286-297.

[91] Id.

[92] Bora, E., & Pantelis, C. (2016). Meta-analysis of social cognition in attention-deficit/hyperactivity disorder (ADHD): Comparison with healthy controls and autistic spectrum disorder. *Psychological Medicine*, *46*(4), 699-716.

[93] Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., ... & Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*, *55*(2), 198-208.

small similarities in the subcortical structures affected by ADHD and ASD, there are no similarities in the structural brain abnormalities measured on MRIs.[94] ADHD symptoms respond to medications, including amphetamine, methylphenidate, alpha-2 agonists and norepinephrine transporter inhibitors. The symptoms of ASD do not respond to these medications. No medication has been found to be markedly effective for the core symptoms of ASD.

### B. Epidemiological Studies Evaluating Acetaminophen Use During Pregnancy and ADHD in Offspring

#### i. Studies Using ADHD Diagnoses with Sibling Controls

69. Unlike other observational epidemiological studies, a sibling control study design accounts for unmeasured familial confounding.[95] A familial confounder is any confounder that is shared by siblings, such as a parent's genetic risk for ADHD.

70. Two research groups have documented that genetic confounding affects observational studies evaluating whether maternal use of acetaminophen during pregnancy is associated with ADHD in offspring. These studies assayed the DNA of mothers and computed their polygenic risk score (PRS) for ADHD. The PRS estimates the risk of ADHD based upon DNA variants in a mother's genome.

71. Leppert et al. (2019) found that maternal PRS for ADHD was statistically significantly associated with maternal acetaminophen use in late pregnancy.[96] The authors state

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[94] Radonjić, N. V., Hess, J. L., Rovira, P., Andreassen, O., Buitelaar, J. K., Ching, C. R., ... & Faraone, S. V. (2021). Structural brain imaging studies offer clues about the effects of the shared genetic etiology among neuropsychiatric disorders. *Molecular Psychiatry*, *26*(6), 2101-2110.

Hoogman, M., Van Rooij, D., Klein, M., Boedhoe, P., Ilioska, I., Li, T., ... & Franke, B. (2022). Consortium neuroscience of attention deficit/hyperactivity disorder and autism spectrum disorder: The ENIGMA adventure. *Human Brain Mapping*, *43*(1), 37-55.

[95] Thapar, A., & Rice, F. (2020). Family-based designs that disentangle inherited factors from pre-and postnatal environmental exposures: In vitro fertilization, discordant sibling pairs, maternal versus paternal comparisons, and adoption designs. *Cold Spring Harbor Perspectives in Medicine, 11*(3), a038877.

[96] Leppert, B., Havdahl, A., Riglin, L., Jones, H. J., Zheng, J., Smith, G. D., ... & Stergiakouli, E. (2019). Association of maternal neurodevelopmental risk alleles with early-life exposures. *JAMA Psychiatry*, *76*(8), 834-842.

that "mothers with higher ADHD PRS may also be more likely to use acetaminophen in pregnancy."[97] This result underscores the necessity of controlling for genetic confounding in studies about maternal acetaminophen exposure during pregnancy and ADHD.

72. Dr. Baccarelli argues that even assuming maternal PRS for ADHD causes prenatal acetaminophen use, that does not mean genetics are "the cause of [a] child's ADHD."[98] Alternatively, he posits that if maternal PRS does not cause prenatal acetaminophen use, "then any possible confounding would be caused by other variables correlated with genetics, such as for instance race or ethnicity, which have been typically controlled for in most studies investigating prenatal acetaminophen and child's ADHD."[99]

73. These arguments are misplaced. The data show that mothers who use acetaminophen during pregnancy have a higher genetic risk for ADHD than other mothers. That means those mothers are more likely to transmit ADHD genomic risk to their offspring—regardless of whether they use acetaminophen during pregnancy—which, in turn, means that their offspring are more likely to have ADHD. Indeed, genetic ADHD risk can independently cause both increased maternal acetaminophen use and child ADHD through inherited genetics. Increased genetic risk causes the mother to have ADHD, which puts her at increased risk for fever, infection, accidents, and painful events, and therefore greater acetaminophen use. She also passes on her genetic risk for ADHD to her offspring, which causes ADHD in the offspring.

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Of note, the same research group reported no significant association between ADHD PRS and maternal APAP in a paper published three years earlier but revised that conclusion after updated analysis.

[97] Leppert, B., Havdahl, A., Riglin, L., Jones, H. J., Zheng, J., Smith, G. D., ... & Stergiakouli, E. (2019). Association of maternal neurodevelopmental risk alleles with early-life exposures. *JAMA Psychiatry*, *76*(8), 834-842 at 839.

[98] Baccarelli Amended Report at 123.

[99] Id.

74. Dr. Baccarelli also argues that genetic risk factors for ADHD might be correlated with measured confounders, such as race and ethnicity.[100] This ignores that the method for creating PRS adjusts for potential confounders of race and ethnicity. In addition, most observational studies acknowledge the possibility of residual confounding, which can include unmeasured genetic factors.

75. Dr. Baccarelli also suggests that a sibling control study is unnecessary because "multiple other studies have addressed this concern by using maternal family history of neurodevelopmental disease as a proxy of genetic confounding."[101] Dr. Baccarelli does not cite any of these "multiple" studies, and my own review of the literature found that three of the studies analyzing clinically diagnosed ADHD appear to have considered or adjusted for maternal ADHD.[102] Each of these studies, however, used weak measures to control for familial and genetic factors.

76. In short, given the well-documented contribution of genetics to ADHD risk, a sibling-controlled study provides the best feasible evidence of whether a genetic confounder artificially elevated the risk between an environmental exposure and ADHD.

77. Only two studies used a sibling control design. **Brandlistuen et al. (2013)** used the Norwegian Mother and Child Cohort (MoBa) database to evaluate the relationship

[100] Id.

[101] Id.

[102] Baker, B. H., Lugo-Candelas, C., Wu, H., Laue, H. E., Boivin, A., Gillet, V., ... & Baccarelli, A. A. (2020). Association of prenatal acetaminophen exposure measured in meconium with risk of attention-deficit/hyperactivity disorder mediated by frontoparietal network brain connectivity. *JAMA Pediatrics*, *174*(11), 1073-1081.

Liew, Z., Ritz, B., Rebordosa, C., Lee, P. C., & Olsen, J. (2014). Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatrics*, *168*(4), 313-320.

Ystrom, E., Gustavson, K., Brandlistuen, R. E., Knudsen, G. P., Magnus, P., Susser, E., ... & Reichborn-Kjennerud, T. (2017). Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics*, *140*(5), e20163840.

between prenatal acetaminophen exposure and several neurodevelopmental effects (but not ADHD diagnoses specifically).[103] The authors used a series of questionnaires to assess "psychomotor development," "behavior," and "temperament." The study concluded that siblings exposed to acetaminophen had some adverse developmental outcomes at 3 years of age relative to unexposed siblings. In particular, while many scores showed no significant association with acetaminophen exposure, siblings exposed for 28 days did show greater "activity" levels as well as greater "internalizing" and "externalizing" behavioral problems and some psychomotor limitations. Those exposed fewer than 28 days showed no significant changes in temperament or behavior.[104] But the meaning of these findings for diagnosed ADHD is entirely unclear. As the authors acknowledged: "Because clinical assessments with diagnostic tools were not available in this study, we could not determine the clinical importance of the difference observed. Future studies should seek to include clinical diagnoses of neurodevelopmental and behavioral diagnoses to explore whether there is an increased risk of, for example, attention deficit hyperactivity disorder[.]"[105]

78. **Gustavson et al. (2021)** also used the MoBa database but with a larger sample (21,448 children) to evaluate whether acetaminophen use during pregnancy causes ADHD in offspring.[106] By contrast to Brandlistuen et al. (2013), the researchers used clinically diagnosed

[103] Brandlistuen, R. E., Ystrom, E., Nulman, I., Koren, G., & Nordeng, H. (2013). Prenatal paracetamol exposure and child neurodevelopment: A sibling-controlled cohort study. *International Journal of Epidemiology, 42*(6), 1702-1713.

[104] Id. at 1708.

[105] Id. at 1711.

[106] Gustavson, K., Ystrom, E., Ask, H., Ask Torvik, F., Hornig, M., Susser, E., ... & Reichborn-Kjennerud, T. (2021). Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder-a longitudinal sibling control study. *JCPP Advances, 1*(2), e12020.

ADHD as the study outcome and accounted for potential genetic confounding by applying a sibling control design.

79. In the study, Norwegian pregnant women between 1999 and 2008 were invited for routine ultrasound examination in gestational week 17. To determine medical conditions and medication exposure, they were also administered maternal questionnaires at gestational weeks 17 and 30 and six months after birth. Information on ADHD diagnoses was obtained from the Norwegian Patient Registry.

80. Risk ratios were computed using two methods: (1) the standard method, which compared children from different mothers and (2) the sibling control method, which compared children from the same mother. When risk ratios using the standard method were computed, an increased risk for ADHD with 29 days or more of acetaminophen exposure was found (RR = 2.02 [95% CI: 1.17-3.25]), but not for one to seven days exposure (RR = 0.87 [95% CI: 0.70-1.08]) or eight to 28 days exposure (RR = 1.13 [95% CI 0.82-1.49]).[107] However, when analyses were conducted using sibling controls, the associations were attenuated (1-7 days, RR = 0.75 [95% CI 0.56 1.03]; 8-28 days, RR = 0.93 [95% CI 0.59 1.46]; >28 days, RR = 1.06 [95% CI 0.51 2.05]).[108] The authors further performed a sensitivity analysis to account for potential forms of bias that can be common in sibling-controlled studies and determined that the attenuation was not due to these biases.[109]

81. Because the sibling-control design adjusts for confounding risk factors that are common to siblings (e.g., family influences, parents' genetic risk for ADHD), this result provides a much less confounded evaluation of the relationship between maternal exposure to

[107] Id. at 7.

[108] Id.

[109] Id. at Appendix S1 and S2, Tables S4-S5, Figures S1, S2.

acetaminophen during pregnancy and ADHD in offspring. Notably, the authors highlighted "the importance of using designs that allow accounting for unmeasured confounding factors when examining prenatal risk factors for neurodevelopmental disorders."[110]

82. The results of Gustavson et al. (2021) are consistent with a long line of research showing that environmental factors once thought to be risk factors for ADHD have no effect when sibling control designs are used. The risks ratios before and after the application of a sibling control design for ADHD risk factors are summarized in the table, below.[111]

| | | Risk Ratios | |
|---|---|---|---|
| **Study**[112] | **Risk Factor** | **Main Analysis** | **Sibling Control Analysis** |
| **Chen 2014** | Maternal Obesity | aHR=1. 64, 95% CI=1.57-1.73 | aHR=1.15, 95% CI=0.85-1.56 |
| **Skoglund 2014** | Maternal smoking (≥10 cig/day) | aRR=2.04, 95% CI=1.95-2.13 | aRR=0.84, 95% CI=0.65-1.06 |

[110] Id. at 8.

[111] aHR stands for adjusted hazard ratio, the risk ratio generated by survival analysis methods.

[112] Chen, Q., Sjölander, A., Långström, N., Rodriguez, A., Serlachius, E., D'Onofrio, B. M., ... & Larsson, H. (2014). Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: A population-based cohort study using a sibling-comparison design. *International Journal of Epidemiology*, *43*(1), 83-90.

Skoglund, C., Chen, Q., D'Onofrio, B. M., Lichtenstein, P., & Larsson, H. (2014). Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. *Journal of Child Psychology and Psychiatry*, *55*(1), 61-68.

Curran, E. A., Khashan, A. S., Dalman, C., Kenny, L. C., Cryan, J. F., Dinan, T. G., & Kearney, P. M. (2016). Obstetric mode of delivery and attention-deficit/hyperactivity disorder: A sibling-matched study. *International Journal of Epidemiology*, *45*(2), 532-542.

Wiggs, K. K., Rickert, M. E., Hernandez-Diaz, S., Bateman, B. T., Almqvist, C., Larsson, H., ... & D'Onofrio, B. M. (2017). A family-based study of the association between labor induction and offspring attention-deficit hyperactivity disorder and low academic achievement. *Behavior Genetics*, *47*, 383-393.

Axelsson, P. B., Clausen, T. D., Petersen, A. H., Hageman, I., Pinborg, A., Kessing, L. V., ... & Løkkegaard, E. C. L. (2019). Investigating the effects of cesarean delivery and antibiotic use in early childhood on risk of later attention deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, *60*(2), 151-159.

Lemelin, M., Sheehy, O., Zhao, J. P., & Bérard, A. (2021). Maternal ADHD medication use during pregnancy and the risk of ADHD in children: Importance of genetic predispositions and impact of using a sibling analysis. *European Neuropsychopharmacology*, *44*, 66-78.

Hegvik, T. A., Klungsøyr, K., Kuja-Halkola, R., Remes, H., Haavik, J., D'Onofrio, B. M., ... & Sariaslan, A. (2023). Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: A cross-national cohort study of 4.5 million individuals and their siblings. *American Journal of Obstetrics and Gynecology*, *228*(2), 233-e1.

See also Gustavson et al. (2017), which does not report risk ratios for the sibling control analysis but instead reports a different measure of the magnitude of the effect, which disappears when sibling controls are used:

Gustavson, K., Ystrom, E., Stoltenberg, C., Susser, E., Surén, P., Magnus, P. & Reichborn-Kjennerud, T. (2017). Smoking in pregnancy and child ADHD. *Pediatrics*, *139*(2), e20162509.

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|---|---|---|---|
| **Curran 2016** | Elective C-section | aHR=1.15, 95% CI=1.11-1.20 | aHR=1.05, 95% CI=0.93-1.18 |
| **Wiggs 2017** | Oxytocin-induced labor induction | aHR=1.23, 95% CI=1.19-1.28 | aHR=0.99, 95% CI=0.91-1.07 |
| **Axelsson 2019** | C-section (intrapartum and prelabor) | $aHR_{IP}$=1.10, 95% CI=1.04-1.16<br>$aHR_{PL}$=1.11, 95% CI=1.05-1.17 | $aHR_{IP}$=1.09, 95% CI=0.97-1.24<br>$aHR_{PL}$=1.03, 95% CI=0.91-1.16 |
| **Lemelin 2021** | Use of ADHD medication | aHR=1.96, 95% CI=1.22-3.15 | aHR=1.14, 95% CI=0.62-1.98 |
| **Hegvik 2023** | Labor epidural analgesia (pooled) | aHR=1.20, 95% CI=1.19-1.21 | aHR=0.99, 95% CI=0.96-1.02 |

83. For example, in their study of labor epidural analgesia, Hegvik and colleagues examined 4,498,462 pregnant women from Finland, Norway, and Sweden between 1987 and 2015. Of that number, 1,091,846 (24.3%) were exposed to epidural analgesia during labor. After pooling and adjusting the data across the three countries, the researchers reported a 20% increased risk for developing ADHD in offspring (aHR = 1.20 (95% CI: 1.19-1.21)). But when the authors performed a sub-cohort sibling analysis, which evaluated 985,444 full siblings who were differentially exposed to labor epidural, 68,991 siblings developed ADHD. Based upon these data, the pooled sibling-comparison risk for epidural use and ADHD was reduced and no longer statistically significant (aHR = 0.99 (95% CI: 0.96-1.02)). As the authors observed: "[W]e found that the associations between labor epidural analgesia and offspring risks of ASD and ADHD were entirely attenuated once we accounted for unmeasured familial confounders (i.e., genetic and early-life environmental influences) shared between biological full siblings who were differentially exposed to labor epidural analgesia."[113]

84. Smoking provides another instructive example. In Thapar et al. (2009), the researchers investigated the relationship between prenatal maternal smoking and ADHD.[114] They concluded:

[113] Hegvik, T. A., Klungsøyr, K., Kuja-Halkola, R., Remes, H., Haavik, J., D'Onofrio, B. M., ... & Sariaslan, A. (2023). Labor epidural analgesia and subsequent risk of offspring autism spectrum disorder and attention-deficit/hyperactivity disorder: a cross-national cohort study of 4.5 million individuals and their siblings. *American Journal of Obstetrics and Gynecology*, *228*(2), 233.e1-233.e12.

[114] Thapar, A., Rice, F., Hay, D., Boivin, J., Langley, K., van den Bree, M., ... & Harold, G. (2009). Prenatal smoking might not cause attention-deficit/hyperactivity disorder: Evidence from a novel design. *Biological Psychiatry*, *66*(8), 722-727.

> "Our findings highlight the need to test causal hypotheses with genetically sensitive designs. Results from traditional observational designs do not necessarily pick up inherited confounds and could therefore be misleading. Our results suggest that the previously observed association between maternal smoking in pregnancy and ADHD might represent an inherited confound."

In an editorial accompanying the study entitled, "*Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims*," Thapar and Rutter observed:

> "Traditionally, epidemiological designs have tended to deal with these two possibilities by adjusting for measured confounders such as social class and parent psychopathology. This type of statistical approach is of course appropriate. However, as highlighted by many, it is problematic because it relies on adequate measurement of the confounding variable and does not deal with unrecognised, unmeasured 'residual' confounding not tapped by the available measures."[115]

85. To assess whether the sibling control results were correct, Thapar et al. (2009)[116] assessed the prenatal smoking/ADHD association in children born to mothers who, due to infertility, required oocyte or embryo donations to become pregnant, and therefore were not genetically related to their children. The authors hypothesized that if prior reports of maternal smoking effects were due to maternal confounds associated with genetics, they should not find a prenatal smoking/ADHD association when mothers and children were not related to each other genetically. After disentangling maternal smoking and maternal ADHD, they found that offspring ADHD was due to the genetic risk of ADHD imparted by the mother, not due to maternal smoking during pregnancy. These results show that the earlier observational epidemiologic studies had come to the wrong conclusion due to unmeasured confounding. The findings also illustrate that sibling-control studies are superior to standard design in testing the validity of posited causes of ADHD.

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[115] Thapar, A., & Rutter, M. (2009). Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims. *The British Journal of Psychiatry*, *195*(2), 100-101.

[116] Thapar, A., & Rutter, M. (2009). Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims. *The British Journal of Psychiatry*, *195*(2), 100-101.

86. Despite this evidence, Dr. Baccarelli argues that sibling-controlled studies generally are flawed if they fail to account for potential familial mediators and moderators. As Dr. Baccarelli explains, "a mediator is a variable that lies along the causal pathway between an exposure and an outcome." I agree that mediators can lead to an underestimate of risk ratios in certain circumstances, but this concern is not relevant to my opinion that maternal genetic risk for ADHD and maternal ADHD have confounded the acetaminophen/ADHD association. There is an established genetic risk for ADHD, which has not been shown to vary based on in utero acetaminophen exposure. As a result, genetics are not a mediator. To be a mediator, acetaminophen exposure itself would have to cause genetic changes that produce ADHD, and Dr. Baccarelli has not cited any study establishing such an effect of acetaminophen exposure. He is simply speculating.

87. Dr. Baccarelli also expresses concern with the sibling control design due to purported moderating variables. Moderation (also called effect modification) means that the impact of the exposure on an outcome depends on the value of a third variable. For moderation to be a problem here, a mother's genetic risk for ADHD would have to change the effect of acetaminophen on a developing fetus. Dr. Baccarelli offers no evidence of any such effects; nor have I seen any such effect described in the literature. His theoretical concern pales in contrast to the fact that the standard design studies have not corrected for all known confounders (e.g., maternal pain, fever, infection, and genetic risk for ADHD). This latter point is documented in the following section.

**ii. Studies Using ADHD Diagnoses Without Sibling Controls**

88. I also considered epidemiological studies that evaluated the relationship between prenatal acetaminophen use and ADHD diagnosis without sibling controls. For the

reasons explained in the previous section, all of these studies are significantly limited because they did not use sibling controls (or perform genetic testing of the study subjects). The studies raise other concerns as well, as I discuss in the table and text below.

89. The table below sets forth studies that presented risk ratios for the diagnosis of ADHD, a questionnaire that asked about the diagnostic criteria for ADHD, or screening tools for ADHD (SDQ or CBCL). A risk ratio measures the increased risk for offspring ADHD among children exposed to acetaminophen in utero. For example, a risk ratio of 2.0 would mean that children who were exposed in utero to acetaminophen are twice as likely to be diagnosed with ADHD. For risk ratios above 1.0, when the lower end of the confidence interval is greater than 1.0, that constitutes a statistically significant association. Of the 14 studies, eight report a statistically significant association between prenatal acetaminophen use and ADHD.

90. When multiple risk ratios were presented in a study, I chose the ratio corresponding to any use of acetaminophen during pregnancy. If risk ratios were given for both diagnoses and questionnaire data, I used the ratio corresponding to the diagnosis of ADHD. If risk ratios at more than one age were provided, I used the ratio for the oldest age, which allows more time for ADHD to emerge and be diagnosed. When I found multiple reports from the same sample, I used studies with larger sample sizes and/or ADHD diagnoses (versus studies which used questionnaires).

91. The risk ratios in each study are adjusted for potential confounders measured by the studies, and the table below indicates whether the analyses were adjusted for three known confounds by indication: maternal fever, pain, and infection during pregnancy. Studies

without an author and date were reported in the Alemany et al. (2021) meta-analysis.[117] I did not use data from Alemany et al. (2021) if data from that study were available in a separate publication.

92. The table excludes studies that did not present risk ratios.[118] These studies were excluded because they do not indicate the degree to which exposure is associated with disorder. An association with increased symptoms could indicate an increase within the range of

[117] Alemany, S., Avella-Garcia, C., Liew, Z., Garcia-Esteban, R., Inoue, K., Cadman, T., ... & Sunyer, J. (2021). Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. *European Journal of Epidemiology*, *36*, 993-1004.

[118] Thompson, J. M., Waldie, K. E., Wall, C. R., Murphy, R., Mitchell, E. A., & ABC Study Group. (2014). Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PloS One*, *9*(9), e108210.

Brandlistuen, R. E., Ystrom, E., Nulman, I., Koren, G., & Nordeng, H. (2013). Prenatal paracetamol exposure and child neurodevelopment: A sibling-controlled cohort study. *International Journal of Epidemiology*, *42*(6), 1702-1713.

Liew, Z., Ritz, B., Virk, J., Arah, O. A., & Olsen, J. (2016). Prenatal use of acetaminophen and child IQ: A Danish cohort study. *Epidemiology*, *27*(6), 912-918.

Liew, Z., Bach, C. C., Asarnow, R. F., Ritz, B., & Olsen, J. (2016). Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. *International Journal of Epidemiology*, *45*(6), 2009-2017.

Vlenterie, R., Wood, M. E., Brandlistuen, R. E., Roeleveld, N., van Gelder, M. M., & Nordeng, H. (2016). Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: A propensity score matched cohort study. *International Journal of Epidemiology*, *45*(6), 1998-2008.

Skovlund, E., Handal, M., Selmer, R., Brandlistuen, R. E., & Skurtveit, S. (2017). Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. *Pharmacoepidemiology and Drug Safety*, *26*(6), 625-634.

Bertoldi, A. D., Rifas-Shiman, S. L., Boing, A. C., da Silva Dal Pizzol, T., Miranda, V. I. A., Silveira, M. P. T., ... & Oken, E. (2020). Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood. *Paediatric and Perinatal Epidemiology*, *34*(3), 267-277.

Golding, J., Gregory, S., Clark, R., Ellis, G., Iles-Caven, Y., & Northstone, K. (2020). Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. *Paediatric and Perinatal Epidemiology*, *34*(3), 257-266.

Parker, S. E., & Werler, M. M. (2020). Prenatal exposure to acetaminophen and neurodevelopment. *Paediatric and Perinatal Epidemiology*, *34*(3), 225-226.

Rifas-Shiman, S. L., Cardenas, A., Hivert, M. F., Tiemeier, H., Bertoldi, A. D., & Oken, E. (2020). Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. *Paediatric and Perinatal Epidemiology*, *34*(3), 287-298.

Trønnes, J. N., Wood, M., Lupattelli, A., Ystrom, E., & Nordeng, H. (2020). Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. *Paediatric and Perinatal Epidemiology*, *34*(3), 247-256.

Bornehag, C. G., Reichenberg, A., Hallerback, M. U., Wikstrom, S., Koch, H. M., Jonsson, B. A., & Swan, S. H. (2018). Prenatal exposure to acetaminophen and children's language development at 30 months. *European Psychiatry*, *51*, 98-103.

normal variation because most children without ADHD have some symptoms of ADHD when questionnaires are used for assessment.

| Study | 95% Confidence Intervals and Risk Ratios | Adjustments | | | Diagnoses |
|---|---|---|---|---|---|
| | | Fever | Pain | Infection | |
| Liew 2014 | 1.37 [1.19, 1.59] | Yes | No | Yes | Yes |
| Gustavson 2021* | 1.06 [0.51, 2.05] | Yes | Yes | Yes | Yes |
| Baker 2020 | 2.43 [1.41, 4.21] | No | No | No | Yes |
| Ji 2020** | 2.86 [1.77, 4.67] - CB<br>2.45 [1.50, 4.03] - MP | Yes<br>Yes | No<br>No | No<br>No | Yes<br>Yes |
| Chen 2019 | 1.20 [1.01, 1.42] | No | No | Yes | Yes |
| Ystrom 2017 | 1.12 [1.02, 1.24] | No | No | No | Yes |
| RHEA | 1.11 [0.29, 4.18] | No | Yes | Yes | No |
| Tovo-Rodrigues 2020 | 0.75 [0.28, 2.01] | No | No | Yes | No |
| GASP | 1.61 [0.84, 3.10] | No | Yes | Yes | No |
| Stergiakouli 2016*** | 1.18 [1.01, 1.38] | Yes | Yes | Yes | No |
| Sznajder 2022 | 1.21 [1.01, 1.45] | No | No | No | No |
| Avella-Garcia 2016 | 1.25 [0.93, 1.69] | Yes | No | Yes | No |
| Liew 2019 | 1.46 [1.01, 2.09] | No | No | No | No |
| Generation R | 1.25 [0.96, 1.62] | No | Yes | Yes | No |

**Note**: *ever exposed not analyzed, 29 days or more use presented here (sibling control); **3rd tertile of exposure; ***supplement eTable2.
Regarding infections, Ji 2020 only adjusted for intrauterine infections and Ystrom 2017 performed stratified analyses for each indication but did not adjust risk ratios.

93. Importantly, an association alone, even one that is statistically significant, does not demonstrate a causal relationship. A statistically significant association simply documents the observation that two events track together. It cannot tell us why they track together. There are at least two interrelated reasons why a statistically significant association between maternal use of acetaminophen and ADHD in offspring would not be considered a true association: (1) the studies lack internal validity; and (2) the lack of internal validity is a particular concern in studies with weak risk ratios.

### iii. Studies of APAP Exposure and ADHD Are Subject to Multiple Serious Internal Validity Limitations

94. In experimental design, "internal validity" refers to the extent to which a research study is free from systematic errors or biases that could affect the accuracy and reliability of its findings. Internal validity is a critical aspect of research because associations identified in a study that lacks internal validity may be spurious. Below I discuss five internal validity concerns that are present in the relevant studies.

95. **Internal Validity Threat #1: Confounding.** As discussed above, confounding occurs when a third factor affects both the exposure and the outcome under study, making it difficult to determine whether the exposure is actually associated with the outcome.[119] This third factor is the "confounder." Here is a simple example. A researcher suspects that drinking more coffee leads to better exam scores. She collects data and finds that students who drink more coffee tend to have higher exam scores. But she also finds that students who drink more coffee are more likely to stay up late studying. Thus, the amount of studying could be the real reason behind the higher exam scores, not the coffee itself. The amount of studying is a confounder because it is related to both the exposure (coffee consumption) and the outcome (exam scores), making it difficult to prove that coffee is truly associated with better exam performance. To understand the true relationship between coffee consumption and exam scores, the researcher would need to account for the confounding factor (the amount of studying) in her analysis. This can be done by using statistical techniques to control for confounding or designing research protocols that minimize the influence of confounders.

[119] Weinberg, C. R. (1993). Toward a clearer definition of confounding. *American Journal of Epidemiology*, *137*(1), 1-8.

96. In experimental studies, confounding factors are controlled by random assignment to treatment and control groups. Random assignment is essential for regulatory approval studies because it controls for all confounds, even those that might be unknown to the investigators. By contrast, observational epidemiology studies rely on statistical methods to adjust for confounders. In other words, the researchers have to come up with a list of potential confounders (e.g., age, genetics, lifestyle habits) and then calculate whether they affect the study results. Observational epidemiology cannot adjust for unmeasurable known confounders or unknown confounders.

97. I have already discussed the possibility of unmeasured familial or genetic confounding. There are many other unmeasured confounders to consider as well. For example, Dr. Hollander's report states: "Additional environmental correlates of ADHD during pregnancy and birth include the presence of maternal stress, maternal hypertension, preeclampsia, maternal obesity, maternal infection, and markers of adversity, including poverty and low socioeconomic status. These environmental insults significantly impact the prenatal environment in part due to mediation by epigenetic processes."[120] No study examining the risk of ADHD in offspring following maternal ingestion of acetaminophen during pregnancy adjusted for all of these potential confounders.

98. After genetics, the most obvious form of confounding in the acetaminophen/ADHD literature is confounding by indication—i.e., where the conditions for which a medication is indicated themselves cause the outcome at issue. Acetaminophen, the medication is indicated for treatment of fever and pain, which often result from infection. None of the studies in the table above adjusted for fever, pain and infection. Five studies did not adjust

[120] Hollander Amended Rep. at 52.

for any of these confounders; three adjusted for one of the confounders; and the rest adjusted for two of these confounders.

99. In addition to familial confounding and confounding by indication, there are many other potential confounders. As the following table shows, although all the studies adjusted their analyses for *some* potential confounders, no study adjusted for all potential confounders.

| **Author** | **Year** | **Confounders Adjusted For** |
|---|---|---|
| Avella-Garcia | 2016 | "region, child gender, age at testing, gestational age at birth, quality of test as rated by the performing psychologist-only for BSID and MSCA, maternal social class, IQ, education and whether the mother reported having any chronic illness, fever or urinary tract infection-not necessarily related to acetaminophen use-during pregnancy; for outcomes at 1 year of age, child age at testing was adjusted for prematurity." |
| Baker | 2020 | "maternal age at birth, maternal body mass index, maternal smoking and alcohol use during pregnancy, maternal educational level, family income, and child sex." |
| Chen | 2019 | "demographic data, gestational infections, comorbid perinatal conditions, and maternal mental health disorders" (major depressive disorder, bipolar disorder, schizophrenia) |
| Gustavson | 2021 | "The medical conditions were classified into five different indication groups: pain conditions, fever/infections, chronic auto-immune or inflammatory conditions, unspecified conditions, and other conditions." |
| Ji | 2020 | "maternal age at delivery, maternal race/ethnicity, maternal educational level, marital status, stress during pregnancy, smoking before or during pregnancy, alcohol use before or during pregnancy, maternal body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), parity, breastfeeding, ever use of illicit drugs, stress during pregnancy, maternal fever during pregnancy, early childhood lead levels, child's sex, delivery type, preterm birth, and birth weight" |
| Liew | 2014 | "child's birth year, birth weight, and sex, as well as maternal age at child's birth, parity, gestational age at delivery, socioeconomic status, smoking and alcohol drinking during pregnancy, prepregnancy body mass index (calculated as weight in kilograms divided by height in meters squared), and mother's self-reported psychiatric illnesses. Women were asked to self-report whether they had psychiatric illnesses and had seen a doctor or psychologist because of depression, anxiety, childhood |

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| | | psychiatric disorder, family problems/life crisis, or other mental health problems. We also considered parent's self-reported childhood behavior problem for the analysis of ADHD-like behaviors (SDQ scale) in children."… "To address potential confounding by indication, we further adjusted for diseases or conditions that may trigger use of acetaminophen during pregnancy: muscle and joint diseases, fever, and inflammation or infections." |
| Liew | 2019 | "maternal age at the child's birth (<30, 30-34, 35-40, or >40 years), child's birth order (first, second, third, or fourth or later), child's birth year (continuous), maternal gestational diabetes (yes/no), preeclampsia (yes/no), and self-reported regular maternal use of aspirin or aspirin-containing medication ... or other nonsteroidal antiinflammatory drugs" ... "Information regarding use of aspirin and other nonsteroidal antiinflammatory drugs was collected in a manner similar to that described above for acetaminophen." |
| Stergiakouli | 2016 | "maternal age at birth, parity, socioeconomic status, smoking and alcohol consumption during pregnancy, prepregnancy body mass index (BMI), maternal self-reported psychiatric illness, and possible indications for acetaminophen use. Mothers were asked to report whether they smoked or consumed alcohol during pregnancy by completing a questionnaire at 32 weeks of pregnancy." ... "At the same time, they were also asked if they had muscle and joint problems, infections (including cold or flu, urinary, or other infections), migraine, or headaches in the previous 3 months." |
| Sznajder | 2022 | "adjusted for trouble sleeping, thyroid conditions, maternal age, insurance coverage, alcohol consumption, diagnosis of anxiety or depression and stress" |
| Tovo-Rodrigues | 2020 | "family wealth index; mother's skin colour; mother's age; mother's schooling; single mothers; parity; pre-pregnancy BMI; tobacco and alcohol use; prenatal care (number of antenatal care appointments attended during pregnancy) during pregnancy; mood symptoms; infectious diseases; high blood pressure and gestational diabetes and treatment received during pregnancy; use of other analgesics during pregnancy; and child sex" |
| Ystrom | 2017 | "birth year, parental ADHD symptoms, alcohol use during pregnancy, smoking during pregnancy, symptoms of anxiety and depression during pregnancy, maternal education, marital status, BMI at 17th week of gestation, maternal age, and parity" |
| GASP | NA | "Maternal characteristics included age at delivery (years), education (low, medium, high), pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and mental health problems (yes/no) during pregnancy, age at birth (years) and |

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|---|---|---|
| | | parity (nulliparous, > 1 and > 2), maternal fever (yes/no) and infections (yes/no) during pregnancy." |
| Generation R | NA | "Maternal characteristics included age at delivery (years), education (low, medium, high), pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and mental health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, > 1 and > 2), maternal fever (yes/no) and infections (yes/no) during pregnancy." |
| RHEA | NA | "Maternal characteristics included age at delivery (years), education (low, medium, high), pre-pregnancy body-mass index (BMI), alcohol (yes/no), smoking (yes/no) and mental health problems (yes/no) during pregnancy, age at birth (years) and parity (nulliparous, > 1 and > 2), maternal fever (yes/no) and infections (yes/no) during pregnancy." |

100. The failure to fully adjust is concerning because use of alcohol or illicit drugs during pregnancy can lead to a range of developmental and behavioral problems, and ADHD is frequently comorbid with alcohol and drug abuse.[121] Mothers who have been injured are more likely to use acetaminophen than other mothers, and it is well-documented that ADHD is associated with an increased risk of accidental injuries.[122] Hypertension during pregnancy can

[121] Estévez-Lamorte, N., Foster, S., Eich-Höchli, D., Moggi, F., Gmel, G., & Mohler-Kuo, M. (2019). Adult attention-deficit/hyperactivity disorder, risky substance use and substance use disorders: A follow-up study among young men. *European Archives of Psychiatry and Clinical Neuroscience*, *269*, 667-679.

Hartman, C. A., Chen, Q., Solberg, B. S., Du Rietz, E., Klungsøyr, K., Cortese, S., ... & Bellato, A. (2023). Anxiety, mood, and substance use disorders in adult men and women with and without attention-deficit/hyperactivity disorder: A substantive and methodological overview. *Neuroscience & Biobehavioral Reviews*, *151*, 105209.

Özgen, H., Spijkerman, R., Noack, M., Holtmann, M., Schellekens, A. S., Van De Glind, G., ... & Hendriks, V. (2020). International consensus statement for the screening, diagnosis, and treatment of adolescents with concurrent attention-deficit/hyperactivity disorder and substance use disorder. *European Addiction Research*, *26*(4-5), 223-232.

Treur, J. L., Demontis, D., Smith, G. D., Sallis, H., Richardson, T. G., Wiers, R. W., ... & Munafò, M. R. (2021). Investigating causality between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization. *Addiction Biology*, *26*(1), e12849.

Yule, A. M., Martelon, M., Faraone, S. V., Carrellas, N., Wilens, T. E., & Biederman, J. (2017). Examining the association between attention deficit hyperactivity disorder and substance use disorders: A familial risk analysis. *Journal of Psychiatric Research*, *85*, 49-55.

[122] Chang, Z., Lichtenstein, P., D'Onofrio, B. M., Sjölander, A., & Larsson, H. (2014). Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: A population-based study. *JAMA Psychiatry*, *71*(3), 319-325.

lead to complications such as preeclampsia, low birth weight, and premature birth, which are risk factors for child ADHD,[123] and adults with ADHD are more likely to have hypertension compared with other adults.[124] Migraine,[125] diabetes,[126] and obesity[127] are each associated with ADHD and

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Swensen, A., Birnbaum, H. G., Hamadi, R. B., Greenberg, P., Cremieux, P. Y., & Secnik, K. (2004). Incidence and costs of accidents among attention-deficit/hyperactivity disorder patients. *Journal of Adolescent Health*, *35*(4), 346-e1-9.

Vaa, T. (2014). ADHD and relative risk of accidents in road traffic: A meta-analysis. *Accident Analysis & Prevention*, *62*, 415-425.

[123] Kim, J. H., Kim, J. Y., Lee, J., Jeong, G. H., Lee, E., Lee, S., ... & Fusar-Poli, P. (2020). Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: An umbrella review. *The Lancet Psychiatry*, *7*(11), 955-970.

[124] Chen, Q., Hartman, C. A., Haavik, J., Harro, J., Klungsøyr, K., Hegvik, T. A., ... & Larsson, H. (2018). Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. *PloS One*, *13*(9), e0204516.

[125] Arruda, M. A., Guidetti, V., Galli, F., Albuquerque, R. C., & Bigal, M. E. (2010). Migraine, tension-type headache, and attention-deficit/hyperactivity disorder in childhood: A population-based study. *Postgraduate Medicine*, *122*(5), 18-26.

Hansen, T. F., Hoeffding, L. K., Kogelman, L., Haspang, T. M., Ullum, H., Sørensen, E., ... & Burgdorf, K. (2018). Comorbidity of migraine with ADHD in adults. *BMC Neurology*, *18*(1), 1-9.

Kutuk, M. O., Tufan, A. E., Guler, G., Yalin, O. O., Altintas, E., Bag, H. G., ... & Ozge, A. (2018). Migraine and associated comorbidities are three times more frequent in children with ADHD and their mothers. *Brain and Development*, *40*(10), 857-864.

Salem, H., Vivas, D., Cao, F., Kazimi, I. F., Teixeira, A. L., & Zeni, C. P. (2018). ADHD is associated with migraine: A systematic review and meta-analysis. *European Child & Adolescent Psychiatry*, *27*, 267-277.

[126] Dehnavi, A. Z., Zhang-James, Y., Draytsel, D., Carguello, B., Faraone, S. V., & Weinstock, R. S. (2023). Association of ADHD symptoms with type 2 diabetes and cardiovascular comorbidities in adults receiving outpatient diabetes care. *Journal of Clinical & Translational Endocrinology*, *32*, 100318.

Baranova, A., Chandhoke, V., Cao, H., & Zhang, F. (2023). Shared genetics and bidirectional causal relationships between type 2 diabetes and attention-deficit/hyperactivity disorder. *General Psychiatry*, *36*(2), e100996.

Mazor-Aronovitch, K., Pinhas-Hamiel, O., Pivko-Levy, D., Modan-Moses, D., Levek, N., Miller, S., ... & Landau, Z. (2021). Dual diagnosis of type 1 diabetes mellitus and attention deficit hyperactivity disorder. *Pediatric Diabetes*, *22*(4), 649-655.

Zeng, Y., Tang, Y., Yue, Y., Li, W., Qiu, X., Hu, P., ... & Mu, D. (2020). Cumulative evidence for association of parental diabetes mellitus and attention-deficit/hyperactivity disorder. *Neuroscience & Biobehavioral Reviews*, *117*, 129-139.

[127] Javaras, K. N., Munn-Chernoff, M. A., Diemer, E. W., Thornton, L. M., Bulik, C. M., Yilmaz, Z., ... & Baker, J. H. (2022). Shared genetic factors contributing to the overlap between attention-deficit/hyperactivity disorder symptoms and overweight/obesity in Swedish adolescent girls and boys. *Twin Research and Human Genetics*, *25*(6), 226-233.

Li, Y. J., Xie, X. N., Lei, X., Li, Y. M., & Lei, X. (2020). Global prevalence of obesity, overweight and underweight in children, adolescents and adults with autism spectrum disorder, attention-deficit hyperactivity disorder: A systematic review and meta-analysis. *Obesity Reviews*, *21*(12), e13123.

each lead to pain which would lead to greater acetaminophen use, which in turn would induce a confounded association between maternal ADHD and acetaminophen use.

101. Given the many potential confounders that are known, together with the problem of unknown confounders and the fact that no study measured or adjusted for known significant confounders, Dr. Baccarelli is incorrect when he writes that "[t]here is ... no credible evidence that confounding or other forms of bias are responsible for the" purported association between acetaminophen use and ADHD. Dr. Baccarelli argues that epidemiological studies have "controlled for maternal age, maternal illness, maternal use of medication, maternal intelligence, parental education levels, child birth weight, child gestational age, socioeconomic status, maternal drinking, maternal smoking, maternal drug use, genetic confounding, confounding due to indication (i.e., the clinical reason for taking the medication), and many other potential risk factors."[128] This is a misleading statement because no study adjusted for all these confounders concurrently and because the list of risk factors does not include all known confounders.

102. In conclusion, confounding is a serious threat to the internal validity of the studies. As two leaders in the field stated: "We highlight that despite current popular belief that prenatal risk factors are important for psychopathology, there are perils in assuming that control for known confounders necessarily allows inference of causal influences. Currently, the majority

Martins-Silva, T., Vaz, J. D. S., Hutz, M. H., Salatino-Oliveira, A., Genro, J. P., Hartwig, F. P., ... & Tovo-Rodrigues, L. (2019). Assessing causality in the association between attention-deficit/hyperactivity disorder and obesity: A Mendelian randomization study. *International Journal of Obesity*, *43*(12), 2500-2508.

Chen, Q., Hartman, C. A., Kuja-Halkola, R., Faraone, S. V., Almqvist, C., & Larsson, H. (2019). Attention-deficit/hyperactivity disorder and clinically diagnosed obesity in adolescence and young adulthood: A register-based study in Sweden. *Psychological Medicine*, *49*(11), 1841-1849.

Cortese, S., Maia, C. R. M., Rohde, L. A., Morcillo-Peñalver, C., & Faraone, S. V. (2014). Prevalence of obesity in attention-deficit/hyperactivity disorder: Study protocol for a systematic review and meta-analysis. *BMJ Open*, *4*(3), e004541.

[128] Baccarelli Amended Rep. at 6.

of evidence on the links between prenatal risk factors and mental health comes from epidemiological/observational studies. We emphasize the need for different types of designs to exclude causality or test for consistency with a causal hypothesis."[129]

103. **Internal Validity Threat #2: Use of Nonspecific Measures.** Many epidemiological studies assessed measures of behavior that are not specific to ADHD instead of using a diagnosis of ADHD as an end point.[130] These studies cannot be relied on in assessing causality because, as discussed above, neurodevelopmental disorders are a heterogeneous group of conditions that must be analyzed independently. As a result, studies that do not focus on ADHD

[129] Thapar, A., Rice, F., Hay, D., Boivin, J., Langley, K., van den Bree, M., ... & Harold, G. (2009). Prenatal smoking might not cause attention-deficit/hyperactivity disorder: Evidence from a novel design. *Biological Psychiatry*, *66*(8), 722-727.

[130] Streissguth, A. P., Treder, R. P., Barr, H. M., Shepard, T. H., Bleyer, W. A., Sampson, P. D., & Martin, D. C. (1987). Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratology*, *35*(2), 211-219.

Brandlistuen, R. E., Ystrom, E., Nulman, I., Koren, G., & Nordeng, H. (2013). Prenatal paracetamol exposure and child neurodevelopment: A sibling-controlled cohort study. *International Journal of Epidemiology*, *42*(6), 1702-1713.

Avella-Garcia, C. B., Julvez, J., Fortuny, J., Rebordosa, C., García-Esteban, R., Galán, I. R., ... & Sunyer, J. (2016). Acetaminophen use in pregnancy and neurodevelopment: Attention function and autism spectrum symptoms. *International Journal of Epidemiology*, *45*(6), 1987-1996.

Stergiakouli, E., Thapar, A., & Smith, G. D. (2016). Association of acetaminophen use during pregnancy with behavioral problems in childhood: Evidence against confounding. *JAMA Pediatrics*, *170*(10), 964-970.

Ystrom, E., Gustavson, K., Brandlistuen, R. E., Knudsen, G. P., Magnus, P., Susser, E., ... & Reichborn-Kjennerud, T. (2017). Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics*, *140*(5) e20163840.

Liew, Z., Kioumourtzoglou, M. A., Roberts, A. L., O'Reilly, É. J., Ascherio, A., & Weisskopf, M. G. (2019). Use of negative control exposure analysis to evaluate confounding: An example of acetaminophen exposure and attention-deficit/hyperactivity disorder in Nurses' Health Study II. *American Journal of Epidemiology*, *188*(4), 768-775.

Tovo-Rodrigues, L., Carpena, M. X., Martins-Silva, T., Santos, I. S., Anselmi, L., Barros, A. J., ... & Matijasevich, A. (2020). Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. *Paediatric and Perinatal Epidemiology*, *34*(3), 278-286.

Inoue, K., Ritz, B., Ernst, A., Tseng, W. L., Yuan, Y., Meng, Q., ... & Liew, Z. (2021). Behavioral problems at age 11 years after prenatal and postnatal exposure to acetaminophen: Parent-reported and self-reported outcomes. *American Journal of Epidemiology*, *190*(6), 1009-1020.

Sznajder, K. K., Teti, D. M., & Kjerulff, K. H. (2022). Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: A prospective cohort study. *PloS One*, *17*(9), e0272593.

specifically are unhelpful to determining whether maternal use of acetaminophen during pregnancy is associated with ADHD in offspring.

104. Six of the studies that purport to inform the evaluation of potential ADHD risk—of the 14 studies for which risk ratios are given in the table above—used questionnaires to assess symptoms associated with ADHD (rather than an actual ADHD diagnosis). These studies have been referred to as proxy studies. In fact, they are not legitimate proxies for an ADHD diagnosis. The proxy method is weak because these studies use questionnaires given to parents to approximate a diagnosis of ADHD—or in many cases to simply identify at-risk patients who would benefit from more detailed evaluation of their symptoms. These methods do not rely on a clinical professional and they do not assess all the criteria required to make a diagnosis as described above.

105. The use of questionnaires to identify supposed cases of ADHD limits the internal validity of the so-called proxy studies. It is generally accepted by leaders in the field of ADHD and in professional guidelines for ADHD that questionnaires should not be used on their own to make a diagnosis of ADHD.[131] A key limitation of questionnaires is the lack of involvement of a clinical professional to confirm a diagnosis using accepted criteria. In addition, the questionnaires typically do not assess whether symptoms are extreme for the child's developmental level, whether the symptoms occur in multiple settings, whether the symptoms are

[131] Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., ... & Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*, *128*, 789-818.

Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., ... & Zurhellen, W. (2019). Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, *144*(4), e20192528.

Pliszka, S., & AACAP Work Group on Quality Issues. (2007). Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(7), 894-921.

better accounted for by another mental disorder, and whether the symptoms began before age 12. Each of these determinations is required by DSM criteria for diagnosing ADHD and can only be made based on the judgment of trained clinicians.

106. In some of the proxy studies, the questionnaires were especially weak because they only asked questions about five or six symptoms out of the 18 symptoms required to be assessed to make a diagnosis of ADHD. For example, the Strengths and Difficulties Questionnaire survey has only five of the 18 items used by trained clinicians to diagnose ADHD. Russell et al. (2013) studied this questionnaire and reported that its "positive predictive value (PPV) was low at 12%, which is to be expected in a population-based sample screening for rare disorders comprising young children."[132] Considering this rating scale is wrong 88% of the time, it is obviously not a suitable proxy for an ADHD diagnosis. Nevertheless, it was used by four of the proxy studies.[133] Similar tools have also been found to have low positive predictive values. Three of the proxy studies used a scale from the Child Behavior Checklist, which purports to assess symptoms of ADHD.[134] This scale has a positive predictive value of only 57% and was described

[132] Russell, G., Rodgers, L. R., & Ford, T. (2013). The strengths and difficulties questionnaire as a predictor of parent-reported diagnosis of autism spectrum disorder and attention deficit hyperactivity disorder. *PloS One*, *8*(12), e80247, p. e80247.

[133] Golding, J., Gregory, S., Clark, R., Ellis, G., Iles-Caven, Y., & Northstone, K. (2020). Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. *Paediatric and Perinatal Epidemiology*, *34*(3), 257-266.

Inoue, K., Ritz, B., Ernst, A., Tseng, W. L., Yuan, Y., Meng, Q., ... & Liew, Z. (2021). Behavioral problems at age 11 years after prenatal and postnatal exposure to acetaminophen: Parent-reported and self-reported outcomes. *American Journal of Epidemiology*, *190*(6), 1009-1020.

Stergiakouli, E., Thapar, A., & Smith, G. D. (2016). Association of acetaminophen use during pregnancy with behavioral problems in childhood: Evidence against confounding. *JAMA Pediatrics*, *170*(10), 964-970.

Tovo-Rodrigues, L., Schneider, B. C., Martins-Silva, T., Del-Ponte, B., Loret de Mola, C., Schuler-Faccini, L., ... & Bertoldi, A. D. (2018). Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. *BMC Psychiatry*, *18*(368), 1-11.

[134] Sznajder, K. K., Teti, D. M., & Kjerulff, K. H. (2022). Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: A prospective cohort study. *PloS One*, *17*(9), e0272593.

as merely "a useful screening instrument for ADHD."[135] In other words, this rating scale is wrong nearly half of the time**.**

107. Proxy measures can create false positive diagnoses that are confounded by some other clinical feature or maternal behavior that is unknown. For example, we know that ADHD symptoms also occur in youth who exhibit antisocial behaviors (e.g., lying, stealing, bullying) and oppositionality (e.g., temper tantrums, defiance, hostility, vindictiveness).[136] Thus, it is likely that false positive diagnoses from proxy measures could be identifying children with those symptoms, not children with ADHD. Because those symptoms are associated with many potential confounders (low social class, parental criminality, parental substance abuse), they could easily lead to confounded results.

108. **Internal Validity Threat #3: Misclassification Bias.** The use of questionnaires creates misclassification bias in epidemiological studies. This approach is especially problematic when the mother rates the child's symptoms and also reports her own use of acetaminophen during pregnancy. Using the same rater to evaluate two behaviors can potentially create a spurious association due to "rater bias," which occurs when the rater's perceptions or beliefs influence the ratings of different behaviors, leading to artificially inflated

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Tovo-Rodrigues, L., Carpena, M. X., Martins-Silva, T., Santos, I. S., Anselmi, L., Barros, A. J., ... & Matijasevich, A. (2020). Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. *Paediatric and Perinatal Epidemiology*, *34*(3), 278-286.

[135] Aebi, M., Winkler Metzke, C., & Steinhausen, H. C. (2010). Accuracy of the DSM-oriented attention problem scale of the child behavior checklist in diagnosing attention-deficit hyperactivity disorder. *Journal of Attention Disorders*, *13*(5), 454-463, p. 454.

[136] Doyle, A. E., & Faraone, S. V. (2002). Familial links between attention deficit hyperactivity disorder, conduct disorder, and bipolar disorder. *Current Psychiatry Reports*, *4*(2), 146-152.

Faraone, S. V., Biederman, J., Jetton, J. G., & Tsuang, M. T. (1997). Attention deficit disorder and conduct disorder: Longitudinal evidence for a familial subtype. *Psychological Medicine*, *27*(2), 291-300.

Faraone, S. V., Biederman, J., & Monuteaux, M. C. (2000). Attention-deficit disorder and conduct disorder in girls: Evidence for a familial subtype. *Biological Psychiatry*, *48*(1), 21-29.

associations between two behaviors. These biases can occur for many reasons. Parental recall biases have been documented in several settings.[137] Maternal ratings of ADHD of one sibling have been shown to be biased by the presence of ADHD in other siblings.[138] Acquiescence bias is the systematic bias to answer "yes" to questionnaire items, regardless of the content of the items. Also, some people are more prone to use medications and medical services than others. That type of bias would lead a mother to take acetaminophen and also to be more likely to ask her child's pediatrician to evaluate her child for ADHD. At the other extreme, some mothers, due to religious or other beliefs, will not use medications or even use the healthcare system. They would not take acetaminophen and their children would never be diagnosed with ADHD even if the children had ADHD.

109. **Internal Validity Threat #4: Multiplicity.** The internal validity of the epidemiologic studies is also threatened by the problem of multiplicity. When evaluating the validity of a statistical association such as that reported for acetaminophen exposure and ADHD, one must take account of the total number of statistical tests conducted by the study and whether plans for statistical testing had been made public prior to the publication of results. The reason for this is that statistical association findings are probabilistic, not definitive. The result of the test is

[137] Stormon, N., & Sexton, C. (2023). Parental recall bias in observational studies: Child dental service use. *International Journal of Paediatric Dentistry*.

Hawkins, J., Hires, C., Dunne, E., & Keenan, L. (2021). Recall and Interviewer Bias in Parental Report of Pediatric Exposure to Aromatic Plant Ingredients in Personal Care Products: Development and Validation of a More Accurate Approach. *Journal of Environmental and Public Health*, *2021*, 9924621.

Infante-Rivard C., Jackes L (2000). Empirical study of parental recall bias. *American Journal of Epidemiology, 152(5),* 480-86.

Kulig M., Bergmann R., Edenharter G., Wahn U (2000). Does allergy in parents depend on allergy in their children? Recall bias in parental questioning of atopic diseases. *Journal of Allergy and Clinical Immunology, 105*(2 Pt. 1), 274-278.

[138] Simonoff, E., Pickles, A., Silberg, JL, Rutter, M., Eaves, L (1998). Genetic influences on childhood hyperactivity: Contrast effects imply parental rating bias, not sibling interaction. *Psychological Medicine, 28(4),* 825-837.

a probability value that indicates the probability of observing the magnitude of association reported if, in truth, there were no association.

110. When the p-value is very low, we conclude that the association is probably real. When there is only one primary outcome, convention dictates that a p-value of 0.05 is sufficient for declaring that the association is probably real. However, as the number of outcomes or variables tested increases, it becomes increasingly likely that one will appear statistically significant just by chance. Thus, when two outcomes are specified as primary, we use a more stringent p-value (0.025). When there are N outcomes we use a p-value threshold of 0.05 divided by N. (Many epidemiologic studies report 95% confidence intervals rather than p-values of 0.05, but the same logic applies.)

111. None of the epidemiologic studies about acetaminophen and ADHD were conducted under a publicly available predefined protocol that listed their primary outcomes. Such a protocol is best practice because it limits the possibility that a research team would test many different outcomes or variables and determine only after seeing the results which ones to highlight in a final publication.[139] In that case, when more than one test is conducted, the proper procedure is to adjust the reported p-values (or confidence intervals) for the number of tests and intervals computed. When that is not performed, the publication has a multiplicity problem, and that is the case for all the studies here.

112. An additional, related issue is that none of the acetaminophen studies considered the entire pregnancy exposome (all exposures to which a fetus might have been exposed) or even the entire portion of the exposome to which they had access. One reason why

[139] In light of the well-known phenomenon of publication bias—i.e., the fact that journals are more likely to publish studies that show an association than those that do not—researchers who test many variables without a predetermined protocol face a temptation to highlight those results that show a statistically-significant association.

the human genomewide association study of ADHD can draw firm conclusions about causal regions of the genome is that it examined the entire genome and adjusted its statistical analyses for the multiplicity issue it created. In contrast, a pregnancy exposome wide study of ADHD has never been conducted. That is understandable because none of these studies had data that covered the entire pregnancy exposome. Yet many of these investigators had access to other exposures but those are not addressed in their papers. This makes it impossible to know if their findings are significant when taking into account the entire exposure, which is in contrast to genomic studies where we use a genomewide significance level for analyses.

113. The multiplicity problem is evident on a smaller scale when some of the published studies are more closely examined. For example, Chen et al. (2019)[140] used two different statistical models to assess the possible association between maternal acetaminophen use and ADHD in offspring, adjusting for demographic data, gestational infections, other perinatal conditions, and maternal mental health disorders. As table 2 shows, this effort resulted in 23 different risk ratios. Although most of the risk ratios are not statistically significant (as indicated by the lack of bold font in the table below), the authors conclude: "Prenatal exposure to acetaminophen was associated with an increased risk of ADHD in offspring, regardless of gestational infections and maternal mental health disorders."

114. Table 2 in Chen et al. (2019) presents 95% confidence intervals. As I indicated earlier in this report, a 95% confidence interval for a single outcome means that researchers are 95% confident that the true risk ratio lies within the interval. But because Chen et al. (2019) did not adjust for testing multiple outcomes, 95% confidence intervals are improper—a

[140] Chen, M. H., Pan, T. L., Wang, P. W., Hsu, J. W., Huang, K. L., Su, T. P., ... & Bai, Y. M. (2019). Prenatal exposure to acetaminophen and the risk of attention-deficit/hyperactivity disorder: A nationwide study in Taiwan. *The Journal of Clinical Psychiatry*, *80*(5), 15264.

higher degree of confidence is required. Correcting for multiplicity makes confidence intervals wider—reflecting greater uncertainty in the result. This is an especially serious problem for small effects because the lower end of the interval is almost 1.0. Widening the interval as needed to adjust for the uncertainty introduced by testing for multiple outcomes could cause it to include 1.0, which would mean that the association is not statistically significant.

**Table 2. Risk Ratios from Chen et al. (2019)**

| Variable | Model 1[b] OR (95% CI) | Model 2[c] OR (95% CI) |
|---|---|---|
| Acetaminophen exposure | | |
| Any trimester | **1.21 (1.02–1.43)** | **1.20 (1.01–1.42)** |
| Period from 3 months before pregnancy to date of last menstrual cycle | 1.07 (0.91–1.26) | 1.06 (0.90–1.25) |
| First trimester | 1.10 (0.93–1.30) | 1.09 (0.92–1.28) |
| Second trimester | **1.21 (1.02–1.43)** | **1.19 (1.00–1.40)** |
| Third trimester | 0.98 (0.84–1.14) | 0.97 (0.83–1.13) |
| Gestational infections | | |
| Any trimester | 0.96 (0.81–1.11) | 0.94 (0.80–1.10) |
| Period from 3 months before pregnancy to date of last menstrual cycle | 1.02 (0.83–1.24) | 1.00 (1.82–1.23) |
| First trimester | 0.96 (0.79–1.16) | 0.97 (0.80–1.18) |
| Second trimester | 0.93 (0.77–1.13) | 0.93 (0.77–1.13) |
| Third trimester | 1.05 (0.88–1.25) | 1.05 (0.88–1.25) |
| Maternal mental health disorders | | |
| Major depressive disorder | | **1.57 (1.10–2.24)** |
| Bipolar disorder | | **2.25 (1.19–4.27)** |
| Schizophrenia | | 1.35 (0.55–3.29) |

[a]Boldface type indicates significant at $P < .05$.
[b]Adjusting for demographic data, gestational infections, and comorbid perinatal conditions.
[c]Adjusting for demographic data, gestational infections, maternal mental health disorders, and comorbid perinatal conditions.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OR = odds ratio.

115. Another example of the multiplicity problem can be seen in the publications by Tovo-Rodrigues and colleagues. In their 2018 study,[141] they reported 48 risk ratios. In their 2020 publication from the same sample,[142] they computed 51 risk ratios. Computing so many risk ratios almost guarantees that one or more of the 95% confidence intervals would be statistically significant.

[141] Tovo-Rodrigues, L., Schneider, B. C., Martins-Silva, T., Del-Ponte, B., Loret de Mola, C., Schuler-Faccini, L., ... & Bertoldi, A. D. (2018). Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. *BMC Psychiatry*, *18*, 1-11.

[142] Tovo-Rodrigues, L., Carpena, M. X., Martins-Silva, T., Santos, I. S., Anselmi, L., Barros, A. J., ... & Matijasevich, A. (2020). Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. *Paediatric and Perinatal Epidemiology*, *34*(3), 278-286.

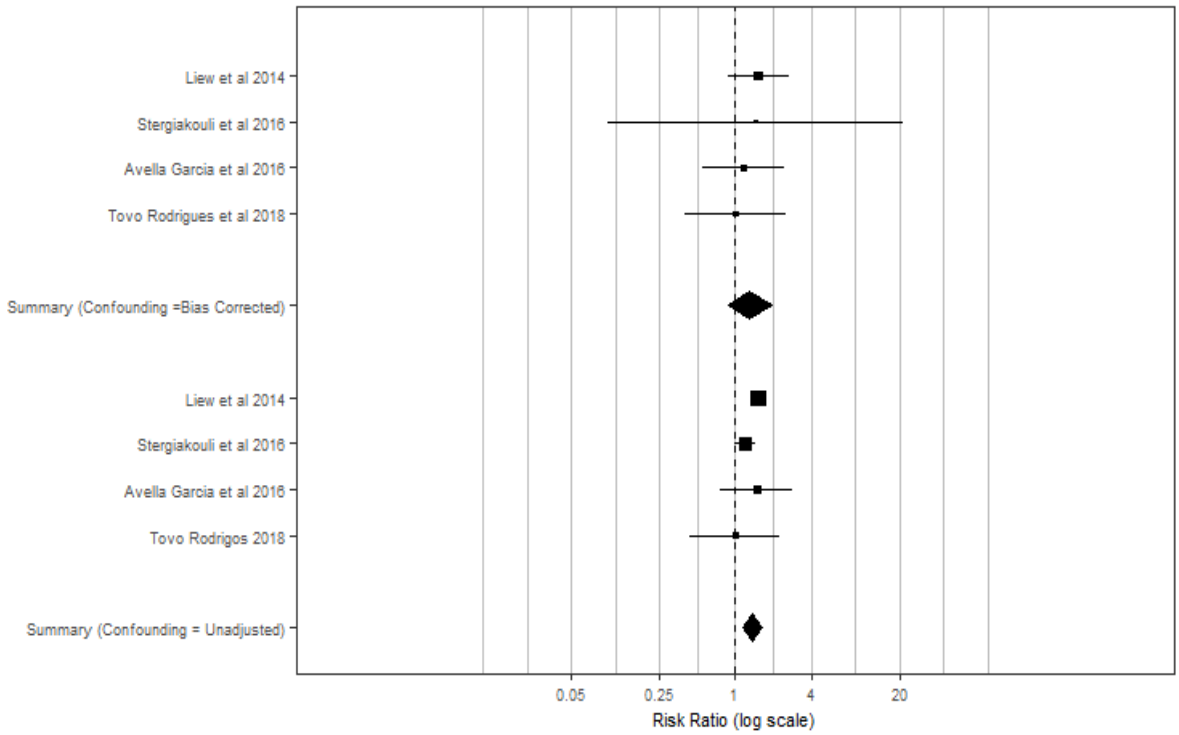
116. Due to these problems that threaten the internal validity of research studies, the use of registered protocols has been widely adopted by regulatory agencies. When researchers register a protocol, they specify all protocol details and the primary outcomes in advance of conducting the study. Although there has been a growing movement to use registered reports and thereby improve the validity of epidemiological data,[143] this approach was not used in any of the observational epidemiology studies of acetaminophen and ADHD.

117. **Internal Validity Threat #5: Selection and Misclassification Biases.** As described by Masarwa et al. (2020),[144] selection bias occurs when "[m]others with co-morbidities resulting in pain and fever medication use may be more or less likely to participate in a study examining the association between acetaminophen and ADHD." This may result in a biased observed effect. Four of the studies in the Masarwa meta-analysis provided sufficient information to correct for selection bias. Masarwa's meta-analysis vividly demonstrates the issue. Before correction, the pooled analysis of the four studies suggested a significant acetaminophen/ADHD association. After correction for selection bias, none of the four studies showed a significant association, and the pooled analysis did not show a significant association. The results can be seen in their e-Figure 4 from their paper, reproduced below. For each study, the plot gives the risk ratio for each study as a point and the 95% confidence interval as horizontal lines around that point. When the 95% confidence interval crosses the dotted vertical line, the result is not significant. The top part of the plot gives the selection bias corrected results. The pooled result is depicted by the black diamond, with the center of the diamond representing the pooled risk ratio and the left and

[143] Chambers, C. D., & Tzavella, L. (2022). The past, present and future of registered reports. *Nature Human Behaviour*, *6*(1), 29-42.

[144] Masarwa, R., Platt, R. W., & Filion, K. B. (2020). Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? *Paediatric and Perinatal Epidemiology*, *34*(3), 309-317.

right edges of the diamond representing the 95% confidence intervals. The pooled result is significant for the original data but not for the bias corrected data. The fact that the 95% confidence intervals are wider for the adjusted data indicates the degree to which selection bias adds uncertainty to the results.




118. Differential misclassification, also known as recall bias, is a serious problem for studies of mental disorders, and can often lead to false positive results. Both the exposure (i.e., acetaminophen use) and the outcome (i.e., ADHD) can be misclassified.

119. With respect to outcome misclassification, recall biases can occur due to increased awareness of psychological problems. If a mother, for example, has had first-hand experience with symptoms of ADHD, she will have a more nuanced understanding of how ADHD manifests, which would lead her to more easily identify ADHD in her children and have them evaluated. A mother with ADHD who has experienced the condition's subtleties—such as difficulty with time management, tendency to interrupt others, or issues with emotional

regulation—might recognize these less commonly known symptoms in her child. For instance, if her child repeatedly struggles to complete tasks in a timely manner, she might identify this as a sign of ADHD.

120. Dr. Baccarelli contends that any misclassification of ADHD symptoms would likely be random, and therefore would bias the results, if at all, toward the null. Specifically, he states that "[d]iagnosis of [neurodevelopmental disorder] is typically performed by health care providers who are expected to be unaware of whether the mothers used acetaminophen during pregnancy. Therefore, any error in the outcome assessment is expected to be independent of the exposure (i.e., non-differential)."[145]

121. While Dr. Baccarelli is correct that a diagnosis of ADHD is performed by a healthcare provider, his statement ignores the fact that most of the studies at issue did not use healthcare provider diagnoses. The studies instead used proxies based on questionnaires that were generally not filled out by a health care professional but rather by a parent or teacher. Even when a diagnosis is made by a health care provider, the report made by the mother can still be biased regardless of whether the health care provider knows about the parent's use of acetaminophen.

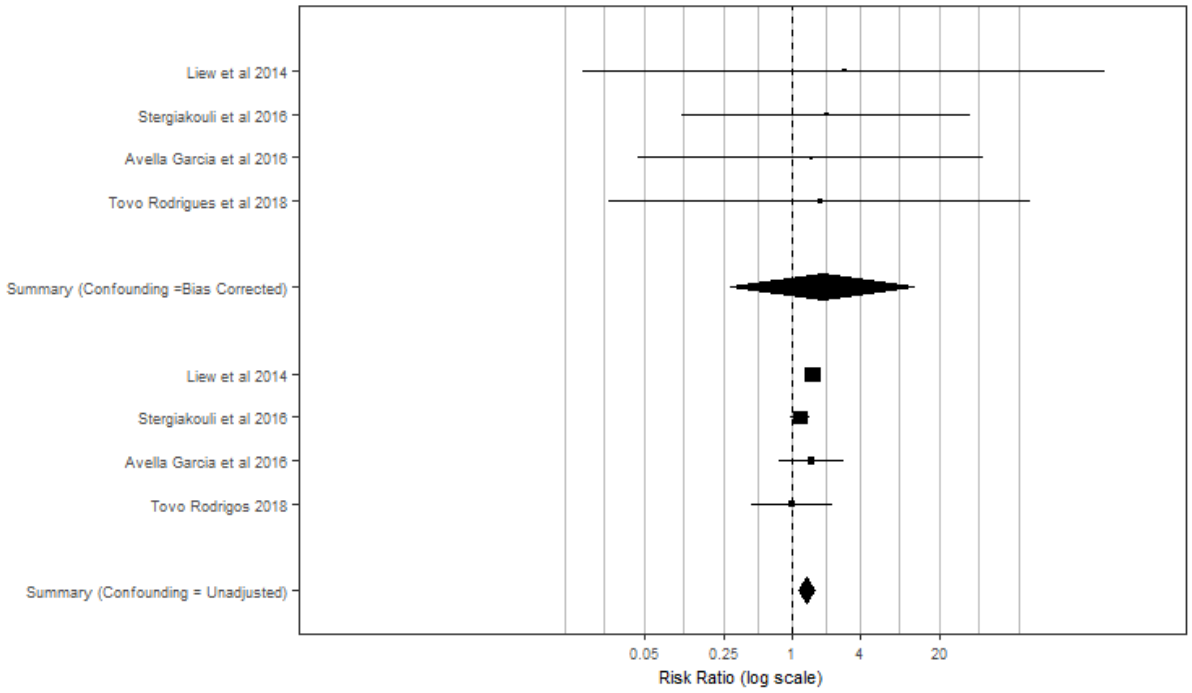
122. Avella-Garcia et al. (2016) addressed the potential for such a bias by using teacher reports of the symptoms of ADHD. They reasoned that, compared with mothers who had not used acetaminophen during pregnancy, mothers who used acetaminophen may respond differently to questions about ADHD in their children. Their data from teachers (RR=1.25 [95% CI 0.93, 1.69]) does not support an association between in utero acetaminophen exposure and offspring ADHD. Their finding is consistent with the theory that confounds related to the mother have confounded other studies.

[145] Baccarelli Amended Rep. at 78.

123. In addition, exposure to acetaminophen in the first instance can be misclassified, creating another source of reporter bias. Women who are at high risk of having children with ADHD (for instance because they have ADHD themselves) may be likely to over-report their use of medication during pregnancy. This could be due, for example, to impulsive responding on a questionnaire or to not being sufficiently attentive to the instructions for providing the information.

124. Four studies in the Masarwa et al. (2020) meta-analysis demonstrate the potential issue. These studies addressed the potential impact of misclassification by simulating a range of sensitivities (how often a true positive is correctly identified) and specificities (how often a true negative is correctly identified). The simulations yield a distribution of bias-adjusted estimates that reflects the potential impact of misclassification. This distribution is summarized (e.g., by calculating the median and 95% percentile interval) to obtain the bias-adjusted association and its uncertainty interval. Before correction for misclassification, the pooled analysis of the four studies suggested a significant association. After correction, no single study showed a significant association, and the pooled analysis did not show a significant association. The results can be seen in e-Figure 5 from their paper, reproduced below. For each study, the plot shows the risk ratio as a point and the 95% confidence interval as horizontal lines around that point. When the 95% confidence interval crosses the dotted vertical line, the result is not significant. The top part of the plot depicts the misclassification bias corrected results. The pooled result is represented by the black diamond, with the center of the diamond representing the pooled risk ratio and the left and right edges of the diamond representing the 95% confidence intervals. The pooled result is significant for the original data but not for the bias corrected data. The fact that the 95% confidence intervals are wider for the adjusted data indicates the degree to which misclassification adds

uncertainty to the results. These misclassification bias analyses are independent of the selection bias and confounder analysis. Each analysis provides a separate assessment of the corresponding biases.




125. After conducting bias analyses, including for selection and misclassification biases, Masarwa et al. (2020) concluded: "Bias analysis suggests that the previously reported association between acetaminophen use during pregnancy and an increased risk of ADHD in the offspring may be due to unmeasured confounding. Our ability to conclude a causal association is limited."[146]

126. Of note, the three other meta-analyses of the association between prenatal use of acetaminophen and offspring ADHD did not adjust for these biases.[147]

[146] Masarwa, R., Platt, R. W., & Filion, K. B. (2020). Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? Paediatric and Perinatal Epidemiology, 34(3), 309-317 at 309.

[147] Alemany, S., Avella-Garcia, C., Liew, Z., Garcia-Esteban, R., Inoue, K., Cadman, T., ... & Sunyer, J. (2021). Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and

127. Several studies used biological measures of acetaminophen exposure to avoid the problems associated with maternal reports of acetaminophen use.[148] These studies help correct for potential maternal exposure misclassification because a biological measure of acetaminophen exposure cannot be affected by maternal reporting biases. But they remain open to all the other problems discussed. The use of a biological measure does not immunize these studies immune from all confounders or from selection and misclassification biases. It only protects them from confounders related to the use of maternal reports to define acetaminophen exposure.

128. In addition to the problem of confounding, the biomarker studies are limited in other ways. Most fundamentally, most of them can only capture peripartum exposure because they are based on samples of maternal blood plasma taken post-partum or umbilical cord plasma collected at birth. Because acetaminophen is metabolized and ultimately eliminated from the body

hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. *European Journal of Epidemiology*, *36*, 993-1004.

Gou, X., Wang, Y., Tang, Y., Qu, Y., Tang, J., Shi, J., ... & Mu, D. (2019). Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. *Australian & New Zealand Journal of Psychiatry*, *53*(3), 195-206.

Ricci, C., Albanese, C. M., Pablo, L. A., Li, J., Fatima, M., Barrett, K., ... & Brown, H. K. (2023). In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis. *Paediatric and Perinatal Epidemiology*, *37*(5), 473-484.

[148] Anand, N. S., Raghavan, R., Wang, G., Hong, X., Azuine, R. E., Pearson, C., ... & Wang, X. (2021). Perinatal acetaminophen exposure and childhood attention-deficit/hyperactivity disorder (ADHD): Exploring the role of umbilical cord plasma metabolites in oxidative stress pathways. *Brain Sciences*, *11*(10), 1302.

Baker, B. H., Lugo-Candelas, C., Wu, H., Laue, H. E., Boivin, A., Gillet, V., ... & Baccarelli, A. A. (2020). Association of prenatal acetaminophen exposure measured in meconium with risk of attention-deficit/hyperactivity disorder mediated by frontoparietal network brain connectivity. *JAMA Pediatrics*, *174*(11), 1073-1081.

Ji, Y., Riley, A. W., Lee, L. C., Hong, X., Wang, G., Tsai, H. J., ... & Wang, X. (2018). Maternal biomarkers of acetaminophen use and offspring attention deficit hyperactivity disorder. *Brain Sciences*, *8*(7), 127.

Ji, Y., Azuine, R. E., Zhang, Y., Hou, W., Hong, X., Wang, G., ... & Wang, X. (2020). Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry*, *77*(2), 180-189.

quite rapidly, exposures taken at or after birth would reflect at most acetaminophen consumed in the last hours of pregnancy and during labor. At least one of the studies acknowledges as much.[149]

129. In addition, the Ji et al. (2018) biomarker study has a very serious multiplicity problem because it computed 144 risk ratios without adjusting for the breadth of comparisons, making it all but certain that some association would appear statistically significant, only by the play of chance. Further, although the authors claim to have documented a dose-response relationship between the acetaminophen plasma levels and ADHD because the risk ratios for above-average exposures were greater than risk ratios for below-average exposures, most of these differences were not statistically significant, as indicated by overlap in the 95% confidence intervals. Ji et al. (2020) and Anand et al. (2021),[150] using the same dataset as Ji et al. (2018),[151] undertook similar analyses based on measuring acetaminophen and its metabolites in cord blood samples. These two reports suffer from the same problems as Ji et al. (2018), although each computed fewer risk ratios (32 risk ratios in each study versus 144) to assess the acetaminophen associations with ADHD and ASD.

130. Baker et al. (2020) assessed acetaminophen levels measured in meconium, the first feces of a newborn infant, in 345 newborns.[152] The authors claim to have shown a dose

[149] Ji, Y., Azuine, R. E., Zhang, Y., Hou, W., Hong, X., Wang, G., ... & Wang, X. (2020). Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry*, *77*(2), 180-189, 188 ("may at most reflect maternal use of acetaminophen during the peripartum period").

[150] Ji, Y., Azuine, R. E., Zhang, Y., Hou, W., Hong, X., Wang, G., ... & Wang, X. (2020). Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry*, *77*(2), 180-189.

Anand, N. S., Raghavan, R., Wang, G., Hong, X., Azuine, R. E., Pearson, C., ... & Wang, X. (2021). Perinatal acetaminophen exposure and childhood attention-deficit/hyperactivity disorder (ADHD): Exploring the role of umbilical cord plasma metabolites in oxidative stress pathways. *Brain Sciences*, *11*(10), 1302.

[151] Ji, Y., Riley, A. W., Lee, L. C., Hong, X., Wang, G., Tsai, H. J., ... & Wang, X. (2018). Maternal biomarkers of acetaminophen use and offspring attention deficit hyperactivity disorder. *Brain Sciences*, *8*(7), 127.

[152] Baker, B. H., Lugo-Candelas, C., Wu, H., Laue, H. E., Boivin, A., Gillet, V., ... & Baccarelli, A. A. (2020). Association of prenatal acetaminophen exposure measured in meconium with risk of attention-

effect, but although the point estimate risk ratio for high acetaminophen levels (3.6) was higher than the point estimate for low acetaminophen levels (1.6), the difference (and hence the dose effect) is not statistically reliable because the confidence intervals of the two risk ratios overlap. In addition, the study authors claim mechanistic support based on the results of functional magnetic resonance imaging (fMRI) for a subsample of 48 children, which focused on connectivity in three "classical brain networks often implicated in ADHD: the default mode, salience/cingulo-opercular, and frontoparietal/central executive networks." These neuroimaging results fail to support the conclusion because a recent meta-analysis of fMRI resting state studies of brain network connectivity in ADHD found no differences between people with and without ADHD.[153]

### C. The Low Risk Ratios Do Not Support Causality Between In utero Acetaminophen Exposure and ADHD

131. As plaintiff expert Dr. Baccarelli concedes: "[t]he greater the magnitude of the association between the exposure and the outcome, the more likely a causal relationship exists."[154] Indeed, Dr. Baccarelli cites an epidemiology textbook recognizing that "[a] strong association can help to rule out hypotheses that the association is entirely due to confounding or other bias."[155]

132. Pooled risk ratios in the published meta-analyses from the relevant epidemiological studies are only 1.21 and 1.34, which are too small to demonstrate causality or

deficit/hyperactivity disorder mediated by frontoparietal network brain connectivity. *JAMA Pediatrics*, *174*(11), 1073-1081.

[153] Cortese, S., Aoki, Y. Y., Itahashi, T., Castellanos, F. X., & Eickhoff, S. B. (2021). Systematic review and meta-analysis: Resting-state functional magnetic resonance imaging studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*(1), 61-75.

[154] Baccarelli Amended Rep. at 24.

[155] Id.

rule out confounding.[156] Dr. Baccarelli asserts that such low risk ratios have been determined to be causal for the association between air pollution and death and that similarly small associations exist for observed causal relationships between smoking and heart disease and secondhand smoke and cancer. But these other associations involve variables measured with very little error, plausible biological mechanisms existed, and issues such as confounding has been well addressed. That cannot be said with respect to the reported association between acetaminophen and ADHD for the reasons set forth in this report. In addition, while Dr. Baccarelli asserts that "[e]xposures that are common can cause high numbers of cases even with small relative risks because the prevalence of the exposure is high in the population," that is irrelevant to whether the acetaminophen/ADHD association is real or the result of confounding or some other factor.

133. A Special News Report titled "Epidemiology Faces Its Limits" that was published in *Science*, one of the premier scientific journals in the world, supports the conclusion that the risk ratios for prenatal acetaminophen exposure and the development of ADHD are too small to be considered causative.[157] The author of that report interviewed several world experts in epidemiology who generally agreed that a risk ratio of less than three or four should not be considered causal. For example:

[156] Alemany, S., Avella-Garcia, C., Liew, Z., Garcia-Esteban, R., Inoue, K., Cadman, T., ... & Sunyer, J. (2021). Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. *European Journal of Epidemiology*, *36*, 993-1004.

Masarwa, R., Levine, H., Gorelik, E., Reif, S., Perlman, A., & Matok, I. (2018). Prenatal exposure to acetaminophen and risk for attention deficit hyperactivity disorder and autistic spectrum disorder: A systematic review, meta-analysis, and meta-regression analysis of cohort studies. *American Journal of Epidemiology*, *187*(8), 1817-1827.

[157] Taubes, G. (1995). Epidemiology Faces Its Limits: The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear—but often yields little certainty. *Science*, *269*(5221), 164-169.

a. The report notes that "Harvard's [Dimitrios] Trichopoulos, opt[s] for a fourfold risk increase as the lower limit."

b. Marcia Angell, a former editor of *The New England Journal of Medicine* is quoted as stating that "[a]s a general rule of thumb, we are looking for a relative risk of three or more [before accepting a paper for publication], particularly if it is biologically implausible or if it's a brand-new finding."

c. Robert Temple, Director of Drug Evaluation at the FDA is quoted at stating: "My basic rule is if the relative risk isn't at least three or four, forget it."

d. Sir Richard Doll of Oxford University has stated that "no single epidemiologic study is persuasive by itself unless the lower limit of its 95% confidence level falls above a threefold increased risk."

134. While plaintiffs' experts suggest that small risk ratios are indicative of causation where they have been observed in many different studies, consistently low risk ratios across multiple studies are not compelling where, as here, each of those studies is subject to the same biases and confounding factors. As noted by David Sackett of Oxford University, who is also quoted in the *Science* article, "[c]onsistency has a catch, after all, it is persuasive only if the studies use different architectures, methodologies, and subject groups and still come up with the same results. If the studies have the same design and if there's an inherent bias, it wouldn't make any difference how many times it's replicated. Bias times 12 is still bias."

135. The pooled risk ratio between maternal acetaminophen exposure during pregnancy and ADHD in offspring is far less than the 3.0 to 4.0 that experts across the world have recognized as the floor for demonstrating a causal association. Such small risk ratios are often explained by bias or confounding, and in this instance, there is strong evidence of confounding

across the various studies. Moreover, the published meta-analyses cannot correct for the confounding and other threats to internal validity inherent in the underlying studies on which they report.[158] In sum, the very small risk ratios reported are likely the result of confounding issues that affect all of the studies generally.

**i. Studies Using Negative Controls**

136. Some studies have used results from "negative controls" to provide evidence for the association between prenatal use of acetaminophen and offspring ADHD. In study design, a negative control group is a group in which no association is expected. The logic in using negative controls in this context is as follows: if acetaminophen use during pregnancy causes ADHD in offspring and is not confounded by other factors, then one would expect to find a significant association between maternal acetaminophen use during pregnancy and offspring ADHD but one would not expect to find a significant association between maternal acetaminophen use after pregnancy and offspring ADHD. Likewise, one would not expect to find a significant association between paternal acetaminophen use and offspring ADHD.

137. This logic, and the conclusions drawn from studies using negative controls, are unreliable in the context of ADHD studies. This is so because the ostensible negative control groups (mothers taking acetaminophen after pregnancy, fathers taking acetaminophen after pregnancy) are not true "negative controls" in the traditional sense used for experimental design. In controlled experimental studies, the negative controls differ from the exposed group only with respect to the exposure being studied. In an observational study, however, the negative controls can differ from the exposed group in many ways that could affect the results. For example, women

[158] Shapiro, S. (1994). Meta-analysis/Shmeta-analysis. *American Journal of Epidemiology*, *140*(9), 771-771.

Shapiro, S. (1997). Is meta-analysis a valid approach to the evaluation of small effects in observational studies?. *Journal of Clinical Epidemiology*, *50*(3), 223-229.

who take acetaminophen during pregnancy differ from women who only used acetaminophen after or outside of pregnancy. Both physicians and other sources of healthcare information caution pregnant women to avoid many medications and to consult their physicians before using medications during pregnancy. Because patients with ADHD (or the genetic risk for ADHD) are more likely to exhibit impulsive behaviors, take actions without fully considering potential risks, and be inattentive to physician recommendations,[159] they are more likely to use acetaminophen during pregnancy. As a result, maternal ADHD, and its attendant genetic risk may be more common in women who use acetaminophen during pregnancy as opposed to those who only use acetaminophen outside of pregnancy, which is a significant confounding factor. In addition, pregnancy changes a woman's body in many ways that can affect medication use and are not accounted for in the negative control studies.

### D. Rodent Studies Do Not Support a Causal Link Between Acetaminophen Exposure and ADHD

138. Several plaintiff experts, including Drs. Cabrera, Pearson and Hollander, rely on rodent studies as supposed evidence of a causal link between exposure to acetaminophen and the development of ADHD. While such studies are valuable for generating hypotheses, observing the behavior of rodents exposed to acetaminophen—an entirely different species that has different and significantly more limited neurological and psychological capacities than humans—cannot explain the effect of acetaminophen exposures on the human brain or human behavior. The rodent studies on which plaintiff experts rely—a number of which involve direct, as opposed to in utero, exposures to acetaminophen—do not address behaviors relevant to the

[159] Schoenfelder, E., Kollins, S. (2016). Topical review: ADHD and health-risk behaviors: Toward prevention and promotion. *Journal of Pediatric Psychiatry, 41(7)*, 735-40.

diagnostic criteria for ADHD, and in some cases, address behaviors and neurological effects that have no connection to any ADHD symptom.

139. The utility of rodent research related to ADHD is limited by the fact that it is impossible to assess the core features of ADHD in rodents and that there is no single or definitive pathophysiology of ADHD. It is therefore not possible to correlate rodent behavior with any particular pathological finding equivalent to ADHD.

140. Published literature acknowledges the problems with using animal studies to draw conclusions about ADHD. In a review of animal models related to ADHD, Wickens et al. (2011) explained: "As a behaviourally defined disorder of unknown aetiology and pathophysiology, ADHD presents special problems for the development of animal models."[160] Plaintiffs' expert Dr. Hollander concedes that "more research needs to be done to find an appropriate animal model of hyperactivity" as it relates to ADHD.[161] As observed by Wickens et al. (2011): "To go from the clinical definition to an animal model requires a definition of the clinical symptoms and some interpretation. The key words 'inattention', 'hyperactivity' and 'impulsivity' have certain meanings to clinicians who work with children. The meaning of these words for researchers developing animal models can be different."[162]

141. Below I discuss these issues in more detail.

**i. Behavioral Studies of Rodents Do Not Address the Diagnostic Criteria for ADHD in Humans**

[160] Wickens, J. R., Hyland, B. I., & Tripp, G. (2011). Animal models to guide clinical drug development in ADHD: Lost in translation?. *British Journal of Pharmacology*, *164*(4), 1107-1128.

[161] Hollander Amended Rep. at 58.

[162] Wickens, J. R., Hyland, B. I., & Tripp, G. (2011). Animal models to guide clinical drug development in ADHD: Lost in translation?. *British Journal of Pharmacology*, *164*(4), 1107-1128.

142. Behavioral studies involving laboratory rats exposed to acetaminophen have measured a large number and variety of rodent behaviors. Rodent studies of acetaminophen administration do not define the "abnormality" of rodent activity levels consistent with the DSM diagnostic criteria for ADHD. Many of the impairments recognized as diagnostic for ADHD arise from how the symptoms affect complex human behaviors, such as riding a bicycle (i.e., ADHD youth have more accidents), driving a car (i.e., ADHD adolescents and adults have more accidents), doing well on exams (i.e., ADHD at all ages leads to poor academic performance), earning a living (i.e., adults with ADHD change jobs frequently), and other uniquely human deficits.[163] Likewise, in ADHD, executive functions of the brain are impaired.[164] These are brain functions that enable people to understand abstract concepts, perform complex sequential tasks, organize, plan, prioritize, regulate emotions, avoid procrastination, and keep track of progress towards goals.[165] These human behaviors cannot be properly evaluated in rodent studies because rodents lack the neurological functioning necessary to engage in such behaviors. Only one of the

[163] Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., ... & Wang, Y. (2021). The World Federation of ADHD International Consensus Statement: 208 evidence-based conclusions about the disorder. *Neuroscience & Biobehavioral Reviews*, *128*, 789-818.

[164] Biederman, J., Monuteaux, M. C., Doyle, A. E., Seidman, L. J., Wilens, T. E., Ferrero, F., ... & Faraone, S. V. (2004). Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. *Journal of Consulting and Clinical Psychology*, *72*(5), 757-66.

Biederman, J., Petty, C., Fried, R., Fontanella, J., Doyle, A. E., Seidman, L. J. & Faraone, S. V. (2005). Functional outcomes associated with self-reported executive function deficits in adults with ADHD. In *2005 AACAP/CACAP Joint Annual Meeting*. AACAP/CACAP: Toronto, Canada.

Biederman, J., Petty, C., Fried, R., Fontanella, J., Doyle, A. E., Seidman, L. J., & Faraone, S. V. (2006). Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *163*(10), 1730-1738.

Antshel, K. M., Faraone, S. V., Maglione, K., Doyle, A. E., Fried, R., Seidman, L. J., & Biederman, J. (2010). Executive functioning in high-IQ adults with ADHD. *Psychological Medicine*, *40*(11), 1909-1918.

[165] Chan, R. C., Shum, D., Toulopoulou, T., & Chen, E. Y. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology*, *23*(2), 201-216.

Biederman, J., Petty, C. R., Fried, R., Black, S., Faneuil, A., Doyle, A. E., ... & Faraone, S. V. (2008). Discordance between psychometric testing and questionnaire-based definitions of executive function deficits in individuals with ADHD. *Journal of Attention Disorders*, *12*(1), 92-102.

rodent behaviors addressed in these studies—activity level—simulates a diagnostic criterion for ADHD (i.e., the symptom of hyperactivity). Measures of activity level in rodents, however, do not include the duration, multi-setting, and impairment criteria that are necessary to diagnose ADHD in people.

143. Because rodent studies cannot test for or observe the diagnostic criteria for ADHD, many rodent studies instead substitute neurobehavioral tests. For example, many acetaminophen rodent studies use "open field locomotor activity" as a proxy for ADHD.[166] This

[166] Saad, A., Hegde, S., Kechichian, T., Gamble, P., Rahman, M., Stutz, S. J., ... & Costantine, M. (2016). Is there a causal relation between maternal acetaminophen administration and ADHD?. *PloS One*, *11*(6), e0157380.

Blecharz-Klin, K., Joniec-Maciejak, I., Jawna, K., Pyrzanowska, J., Piechal, A., Wawer, A., & Widy-Tyszkiewicz, E. (2015). Developmental exposure to paracetamol causes biochemical alterations in medulla oblongata. *Environmental Toxicology and Pharmacology*, *40*(2), 369-374.

Philippot, G., Hosseini, K., Yakub, A., Mhajar, Y., Hamid, M., Buratovic, S., & Fredriksson, R. (2022). Paracetamol (acetaminophen) and its effect on the developing mouse brain. *Frontiers in Toxicology*, *4*, 867748.

Philippot, G., Hallgren, S., Gordh, T., Fredriksson, A., Fredriksson, R., & Viberg, H. (2018). A cannabinoid receptor type 1 (CB1R) agonist enhances the developmental neurotoxicity of acetaminophen (paracetamol). *Toxicological Sciences*, *166*(1), 203-212.

Philippot, G., Gordh, T., Fredriksson, A., & Viberg, H. (2017). Adult neurobehavioral alterations in male and female mice following developmental exposure to paracetamol (acetaminophen): Characterization of a critical period. *Journal of Applied Toxicology*, *37*(10), 1174-1181.

Viberg, H., Eriksson, P., Gordh, T., & Fredriksson, A. (2014). Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicological Sciences*, *138*(1), 139-147.

Saeedan, A. S., Singh, I., Ansari, M. N., Singh, M., Rawat, J. K., Devi, U., ... & Kaithwas, G. (2018). Effect of early natal supplementation of paracetamol on attenuation of exotoxin/endotoxin induced pyrexia and precipitation of autistic like features in albino rats. *Inflammopharmacology*, *26*, 951-961.

Zhao, W. X., Zhang, J. H., Cao, J. B., Wang, W., Wang, D. X., Zhang, X. Y., ... & Mi, W. D. (2017). Acetaminophen attenuates lipopolysaccharide-induced cognitive impairment through antioxidant activity. *Journal of Neuroinflammation*, *14*, 1-15.

Kirsten, T. B., Cabral, D., Galvão, M. C., Monteiro, R., Bondan, E. F., & Bernardi, M. M. (2020). Zinc, but not paracetamol, prevents depressive-like behavior and sickness behavior, and inhibits interferon-gamma and astrogliosis in rats. *Brain, Behavior, and Immunity*, *87*, 489-497.

Chen, M. H., Hsu, J. W., Huang, K. L., Bai, Y. M., Ko, N. Y., Su, T. P., ... & Chen, T. J. (2018). Sexually transmitted infection among adolescents and young adults with attention-deficit/hyperactivity disorder: A nationwide longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(1), 48-53.

Umathe, S. N., Manna, S. S., Utturwar, K. S., & Jain, N. S. (2009). Endocannabinoids mediate anxiolytic-like effect of acetaminophen via CB1 receptors. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(7), 1191-1199.

test simply measures rodent activity in an open area where rodents are free to move about quickly, slowly, or not at all. The "open field locomotor activity" is presumably meant to be a rough approximation of the hyperactivity used to define ADHD, but it is only relevant to one of the 18 symptoms ("Is often 'on the go' acting as if 'driven by a motor'") used to diagnose ADHD in humans. As observed by Wickens et al. (2011): "open-field behaviour is arguably not a good measure of the ADHD phenotype: the locomotor activity of children measured in a clinical playroom in terms of grid line crossings has not correlated significantly with parent ratings of hyperactivity, or clinical diagnosis. Therefore, the open-field test has poor reliability as a measure of hyperactivity in the [spontaneously hypertensive rat] and the face validity of the open field test for ADHD is questionable."[167] Open field locomotor activity by rodents also has no relationship to the other documented symptoms of hyperactivity in humans, such as "[o]ften fidgets or taps hands or feet or squirms in seat" and "[o]ften leaves seat in situations where seating is expected."

Rigobello, C., Klein, R. M., Debiasi, J. D., Ursini, L. G., Michelin, A. P., Matsumoto, A. K., ... & Moreira, E. G. (2021). Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. *Behavioural Brain Research*, *408*, 113294.

Suda, N., Cendejas Hernandez, J., Poulton, J., Jones, J. P., Konsoula, Z., Smith, C., & Parker, W. (2021). Therapeutic doses of acetaminophen with co-administration of cysteine and mannitol during early development result in long term behavioral changes in laboratory rats. *Plos One*, *16*(6), e0253543.

Zaitone, S. A., El-Wakeil, A. F., & Abou-El-Ela, S. H. (2012). Inhibition of fatty acid amide hydrolase by URB597 attenuates the anxiolytic-like effect of acetaminophen in the mouse elevated plus-maze test. *Behavioural Pharmacology*, *23*(4), 417-425.

[167] Wickens, J. R., Hyland, B. I., & Tripp, G. (2011). Animal models to guide clinical drug development in ADHD: Lost in translation?. *British Journal of Pharmacology*, *164*(4), 1107-1128.

Barkley, R. A., & Ullman, D. G. (1975). A comparison of objective measures of activity and distractibility in hyperactive and nonhyperactive children. *Journal of Abnormal Child Psychology*, *3*, 231-244.

Routh, D. K., & Schroeder, C. S. (1976). Standardized playroom measures as indices of hyperactivity. *Journal of Abnormal Child Psychology*, *4*, 199-207.

Schroeder, S. R., Milar, C., Wool, R., & Routh, D. K. (1980). Multiple measurement, transsituational diagnosis, and the concept of generalized overactivity. *Journal of Pediatric Psychology*, *5*(4), 365-375.

Similarly, open field locomotor activity in rodents has no reliable connection to the impulsivity and inattentiveness experienced by people with ADHD.[168]

144. Many of the other rodent studies cited by plaintiffs' experts do not address ADHD symptoms and instead observe other behaviors. For example, Dr. Cabrera relies upon findings in Díaz-Estrada et al. (2020) "that APAP disrupted neurotypical heterosexual behavior in rats" such that male rates exposed to acetaminophen in utero "show increased homosexual mounting."[169] Sexual preference has no relationship to ADHD. Similarly, Dr. Cabrera relies on Hay-Schmidt et al. (2017), which addresses changes in the sexual behavior of male rats exposed to acetaminophen, including the likelihood of ejaculation during sex with female rats. This outcome has no bearing on any symptom or diagnostic criteria for ADHD. Dr. Cabrera relies on Harshaw et al. (2022), which purportedly links acetaminophen exposure to "anxiety-related behavior" in female rodents and "males showing elevated levels of avoidance of unfamiliar social partners," neither of which are diagnostic criteria for ADHD.[170] Other studies cited by plaintiff experts, including Gould et al. (2012), address purported changes in the typical rodent behavior of "marble burying" after acetaminophen exposure.[171] Marble burying is a behavior unique to rodents and has no demonstrated connection to ADHD in humans. Dr. Cabrera acknowledges that

[168] Studies of rodent activity levels are further confounded using different locomotion measures among laboratories, making their results even less reliable. For example, Philippot et al. (2017) assesses mouse activity while the mice are in their cages rather than in an open field.

Philippot, G., Gordh, T., Fredriksson, A., & Viberg, H. (2017). Adult neurobehavioral alterations in male and female mice following developmental exposure to paracetamol (acetaminophen): Characterization of a critical period. *Journal of Applied Toxicology*, *37*(10), 1174-1181.

[169] Cabrera Amended Rep. at 103.

[170] Cabrera Amended Rep.at 87.

[171] Cabrera Amended Rep. at 82.

Gould et al. (2012) found that acetaminophen exposure only affected marble burying behavior in some mouse strains and not others.[172]

145. Dr. Cabrera relies on Klein et al. (2020), which states: "This study was the first to evaluate possible neurobehavioral alterations in the pre-pubertal rats exposed to [acetaminophen] during early stages of development. The results point to a phenotype of olfactory losses, reduced emotionality and increased locomotion in females exposed to the drug during pregnancy. … Such changes are relevant to neurodevelopmental disorders such as ASD and ADHD."[173] The behaviors evaluated by Klein et al. (2020) are not ADHD behaviors. Reduced emotionality and olfactory losses are not symptoms of ADHD. To the contrary, youth with ADHD show increased emotionality.[174] The only rat behavior Klein et al. (2020) assess that could potentially be related to ADHD is "time spent in locomotion," but there is no reliable evidence that the time a rat spends in locomotion can be extrapolated to hyperactivity of human children with ADHD. Moreover, the time spent in locomotion observed in Klein et al. (2020) did not differ between rats that had been exposed to acetaminophen in utero and non-exposed rats, yet the investigators concluded that their findings were relevant to ADHD.

146. Another study, Rigobello et al. (2021), reports that in utero acetaminophen exposure increases the dopamine response when the rats received apomorphine after birth.[175]

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[172] Id.

[173] Klein, R. M., Rigobello, C., Vidigal, C. B., Moura, K. F., Barbosa, D. S., Gerardin, D. C. C., ... & Moreira, E. G. (2020). Gestational exposure to paracetamol in rats induces neurofunctional alterations in the progeny. *Neurotoxicology and Teratology*, *77*, 106838, p. 7.

[174] Faraone, S. V., Rostain, A. L., Blader, J., Busch, B., Childress, A. C., Connor, D. F., & Newcorn, J. H. (2019). Practitioner Review: Emotional dysregulation in attention-deficit/hyperactivity disorder-implications for clinical recognition and intervention. *Journal of Child Psychology and Psychiatry*, *60*(2), 133-150.

[175] Rigobello, C., Klein, R. M., Debiasi, J. D., Ursini, L. G., Michelin, A. P., Matsumoto, A. K., ... & Moreira, E. G. (2021). Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. *Behavioural Brain Research*, *408*, 113294.

Because the experiment also exposed rats to both acetaminophen and apomorphine simultaneously, the study does not appropriately simulate the human experience of in utero acetaminophen exposure alone. Similar to Klein et al. (2020), the only rodent behavior assessed in Rigobello et al. (2021) that is potentially related to ADHD is activity level, but the results were inconsistent: acetaminophen-exposed male rats exhibited more activity than non-exposed controls, but the female rats did not.

147. Plaintiff experts cite Philippot et al. (2022), which studied activity level, memory, learning, and cognitive flexibility of acetaminophen-exposed rats but ignored the cardinal symptoms of ADHD: inattention and impulsivity.[176] The results with respect to activity level, the only behavior potentially relevant to ADHD,[177] were inconsistent. Although the authors observed a weak association between acetaminophen exposure in rats and increased activity compared with controls, it was only during the last 30 minutes of a 90-minute session. Philippot et al. (2017) found that both female and male mice exposed to acetaminophen were significantly less active compared with their respective controls during the first 20 minutes of testing for locomotion and total activity,[178] while the same mice showed a significant increase in activity compared to their respective controls during the last 20 minutes of testing. According to Philippot et al. (2017), the data suggest that that acetaminophen-exposed mice show a "disruption of normal habituation capability," with "habituation" referring to a situation in which mice, when placed in a novel environment, require approximately 20 minutes to get accustomed to it before moving about and

[176] Philippot, G., Hosseini, K., Yakub, A., Mhajar, Y., Hamid, M., Buratovic, S., & Fredriksson, R. (2022). Paracetamol (acetaminophen) and its effect on the developing mouse brain. *Frontiers in Toxicology*, *4*, 867748.

[177] Because problems with memory, learning, and cognitive flexibility are not part of the diagnostic criteria for ADHD, these findings cannot be extrapolated to people diagnosed with ADHD.

[178] Philippot, G., Gordh, T., Fredriksson, A., & Viberg, H. (2017). Adult neurobehavioral alterations in male and female mice following developmental exposure to paracetamol (acetaminophen): Characterization of a critical period. *Journal of Applied Toxicology*, *37*(10), 1174-1181.

exploring that environment. The authors state that "disruption of normal habituation capability is considered a disturbance in cognitive function." Disruption of "habituation" is not a diagnostic criterion for ADHD in humans. Moreover, there is no evidence that "habituation," which is seen in other neuropsychiatric disorders, is relevant to the complex executive functions impaired in ADHD.[179] Philippot et al. (2017) acknowledges that "rodent models cannot fully recapitulate complex human neuropsychiatric disorders[.]"[180]

148. In summary, the behavioral studies of rodents exposed to acetaminophen do not address the diagnostic criteria or complex human symptoms of ADHD. It is not scientifically valid to rely upon data from acetaminophen rodent studies as evidence that maternal ingestion of acetaminophen during pregnancy is associated with ADHD in offspring.

149. Animal experiments in the context of ADHD are also problematic because the failure to adjust for multiplicity is often extreme.[181] None of these investigators pre-registered

[179] McDiarmid, T. A., Bernardos, A. C., & Rankin, C. H. (2017). Habituation is altered in neuropsychiatric disorders—A comprehensive review with recommendations for experimental design and analysis. *Neuroscience & Biobehavioral Reviews*, *80*, 286-305.

[180] Philippot, G., Gordh, T., Fredriksson, A., & Viberg, H. (2017). Adult neurobehavioral alterations in male and female mice following developmental exposure to paracetamol (acetaminophen): Characterization of a critical period. *Journal of Applied Toxicology*, *37*(10), 1174-1181.

[181] Klein, R. M., Rigobello, C., Vidigal, C. B., Moura, K. F., Barbosa, D. S., Gerardin, D. C. C., ... & Moreira, E. G. (2020). Gestational exposure to paracetamol in rats induces neurofunctional alterations in the progeny. *Neurotoxicology and Teratology*, *77*, 106838.

Rigobello, C., Klein, R. M., Debiasi, J. D., Ursini, L. G., Michelin, A. P., Matsumoto, A. K., ... & Moreira, E. G. (2021). Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. *Behavioural Brain Research*, *408*, 113294.

Koehn, L., Habgood, M., Huang, Y., Dziegielewska, K., & Saunders, N. (2019). Determinants of drug entry into the developing brain. *F1000Research*, *8*, 1372.

Koehn, L. M., Huang, Y., Habgood, M. D., Kysenius, K., Crouch, P. J., Dziegielewska, K. M., & Saunders, N. R. (2020). Effects of paracetamol (acetaminophen) on gene expression and permeability properties of the rat placenta and fetal brain. *F1000Research*, *9*, 573.

Moungmaithong, S., Leung, B. W., Sahota, D. S., Wang, C. C., Leung, T. Y., & Poon, L. C. (2022). Assessment of embryo morphology following perinatal exposure to aspirin, ibuprofen and paracetamol using whole embryo culture system. *The Journal of Maternal-Fetal & Neonatal Medicine*, *35*(25), 8786-8793.

Saad, A., Hegde, S., Kechichian, T., Gamble, P., Rahman, M., Stutz, S. J., ... & Costantine, M. (2016). Is there a causal relation between maternal acetaminophen administration and ADHD?. *PloS One*, *11*(6), e0157380.

their experimental protocols, leaving open the question of whether other statistical tests were conducted but not published. However, the published studies report that large numbers of tests were conducted within each study, making it likely that false positive findings have been reported, as reflected in the table, below.

| Lead Author | Year | Animal | # of Stat Tests | Correction for Multiplicity? |
|---|---|---|---|---|
| **PRE-NATAL** | | | | |
| Baker | 2023 | Mice | 9 | Yes |
| Blecharz-Klin | 2015 | Rats | 34 | No |
| Blecharz-Klin | 2015 | Rats | 50 | No |
| Blecharz-Klin | 2016 | Rats | 34 | No |
| Blecharz-Klin | 2017 | Rats | 57 | No |
| Klein | 2020 | Rats | 38 | Yes |
| Koehn | 2019 | Rats | 32 | No |
| Koehn | 2020 | Rats | 200 | No |
| Koehn | 2021 | Rats | 16 | No |
| Moungmaithong | 2021 | Mice | 66 | Yes |
| Rigobello | 2021 | Rats | 80 | Yes |
| Saad | 2016 | Mice | 19 | Yes |
| **POST-NATAL UP TO PND14** | | | | |
| Harshaw | 2022 | Mice | 24 | Yes |
| Philippot | 2017 | Mice | 6 | Yes |
| Philippot | 2018 | Mice | 11 | No |
| Philippot | 2021 | Mice | 6 | No |
| Philippot | 2022 | Mice | 8 | No |
| Viberg | 2014 | Mice | 8 | No |

Harshaw, C., & Warner, A. G. (2022). Interleukin-1β-induced inflammation and acetaminophen during infancy: Distinct and interactive effects on social-emotional and repetitive behavior in C57BL/6J mice. *Pharmacology Biochemistry and Behavior*, *220*, 173463.

Philippot, G., Hallgren, S., Gordh, T., Fredriksson, A., Fredriksson, R., & Viberg, H. (2018). A cannabinoid receptor type 1 (CB1R) agonist enhances the developmental neurotoxicity of acetaminophen (paracetamol). *Toxicological Sciences*, *166*(1), 203-212.

**ii. Purported Neurochemistry Changes in Rodents Exposed to Acetaminophen Cannot Be Extrapolated to Humans**

150. Some studies also report changes in brain neurochemistry of rodents exposed to acetaminophen in utero versus non-exposed rodents. Because there is no clear brain lesion or pathophysiology in ADHD, these changes cannot be correlated to humans with ADHD.

151. The human brain and the rodent brain differ in several important ways, ranging from size and structure to function and complexity. These differences affect how the brain processes information and responds to stimuli. The human brain is substantially larger, containing approximately 86 billion neurons compared to 71 million for the house mouse (over 1,200 times fewer) and 200 million for the brown rat (430 times fewer).[182] It is not possible to extrapolate observations of the rodent brain to the human brain given the significant differences in the magnitude of brain volume, neuronal circuitry, and neuronal count.

152. Another important difference between the human brain and the rodent brain is the structure and organization of the cortex. The cortex regulates the cognitive functions that differentiate humans from other species. When comparing humans and rodents, there are differences in the number and organization of cortical areas, as well as the connectivity between them. Most important, humans have a much larger prefrontal cortex ("PFC") than rodents, which regulates the executive functions that are often impaired in people with ADHD. Compared with rodents, humans have a much greater capacity for abstract reasoning and problem-solving, which is thought to be related to the evolution of the PFC and other areas involved in executive functions.

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[182] Herculano-Houzel, S. (2009). The human brain in numbers: A linearly scaled-up primate brain. *Frontiers in Human Neuroscience, 3*, 31.

Herculano-Houzel, S., Mota, B., & Lent, R. (2006). Cellular scaling rules for rodent brains. *Proceedings of the National Academy of Sciences, 103*(32), 12138-12143.

Herculano-Houzel, S., & Lent, R. (2005). Isotropic fractionator: a simple, rapid method for the quantification of total cell and neuron numbers in the brain. *Journal of Neuroscience, 25*(10), 2518-2521.

153. The types of behavior that define ADHD are complex and require the activity of the PFC. A useful biological animal model of ADHD would thus require study of a species with an equivalent PFC. But it is well known that certain regions of the human PFC, specifically those involving high-level cognitive processes, do not exist in rodents.[183] In addition, the interconnections among various parts of the brain differ between primates (including humans) and rodents.[184] According to the literature, "there has been no consensus on the terms used to describe the rodent prefrontal cortex (PFC) or how it relates to the PFC of monkeys and humans."[185]

154. Neurochemical studies of the rodent brain following exposure to acetaminophen generally address its purported effects on the dopamine system. Dopamine is a chemical transmitter in the brain that allows brain cells to communicate with one another. Rigobello et al. (2021) report that in utero acetaminophen exposure increases the dopamine response when rats are also injected with apomorphine.[186] Similarly, Klein et al. (2020) report that in utero acetaminophen exposure causes "increased responsivity of the dopaminergic system."[187] But an increased responsivity of the dopaminergic system is not part of the pathophysiology of ADHD. Although Rigobello et al. (2021) state that "alterations in dopaminergic pathways are

[183] Laubach, M., Amarante, L. M., Swanson, K., & White, S. R. (2018). What, if anything, is rodent prefrontal cortex?. *eNeuro*, *5*(5), e0315-18.2018.

[184] Preuss, T. M. (1995). Do rats have prefrontal cortex? The Rose-Woolsey-Akert program reconsidered. *Journal of Cognitive Neuroscience*, *7*(1), 1-24.

[185] Laubach, M., Amarante, L. M., Swanson, K., & White, S. R. (2018). What, if anything, is rodent prefrontal cortex?. *eNeuro*, *5*(5), e0315-18.2018.

[186] Rigobello, C., Klein, R. M., Debiasi, J. D., Ursini, L. G., Michelin, A. P., Matsumoto, A. K., ... & Moreira, E. G. (2021). Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. *Behavioural Brain Research*, *408*, 113294.

[187] Klein, R. M., Rigobello, C., Vidigal, C. B., Moura, K. F., Barbosa, D. S., Gerardin, D. C. C., ... & Moreira, E. G. (2020). Gestational exposure to paracetamol in rats induces neurofunctional alterations in the progeny. *Neurotoxicology and Teratology*, *77*, 106838.

implicated in the pathophysiology of ADHD,"[188] this statement is misleading. While it is true that that the neuropsychopharmacology of ADHD supports the relevance of dopamine,[189] this does not mean that any "alterations" of the dopamine system are relevant to ADHD.

155. Some have advanced the hypothesis that people with ADHD may have too many dopamine transporters in some brain cells. The rodent models do not address this hypothesis. The dopamine transporter hypothesis derives from: (1) neuroimaging studies that document excess dopamine transporters among patients with ADHD;[190] and (2) the fact that two of the drug classes that treat ADHD patients, methylphenidate and amphetamine, affect the transmission of dopamine by blocking the dopamine transporter.[191] But no researcher has proven or established the validity of the dopamine transporter hypothesis. Thus, there is no reliable scientific evidence that changes in the dopamine system cause ADHD, and therefore dopamine findings from rodent research,

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[188] Rigobello, C., Klein, R. M., Debiasi, J. D., Ursini, L. G., Michelin, A. P., Matsumoto, A. K., ... & Moreira, E. G. (2021). Perinatal exposure to paracetamol: Dose and sex-dependent effects in behaviour and brain's oxidative stress markers in progeny. *Behavioural Brain Research*, *408*, 113294.

[189] Faraone, S. V. (2018). The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neuroscience & Biobehavioral Reviews*, *87*, 255-270.

Faraone, S. V., Bhide, P. G., & Biederman, J. (2018). Neurobiology of attention deficit hyperactivity disorder. Animal and human studies. *Charney & Nestler's Neurobiology of Mental Illness*, pp. 865-878. Oxford University Press.

Faraone, S. V., & Biederman, J. (1998). Neurobiology of attention-deficit hyperactivity disorder. *Biological Psychiatry*, *44*(10), 951-958.

Faraone, S. V. & Biederman, J. (1999). The neurobiology of attention deficit hyperactivity disorder. *Charney & Nestler's Neurobiology of Mental Illness*, pp. 788-801. Oxford University Press.

Faraone, S. V. & Biederman, J. (2004). Neurobiology of attention deficit hyperactivity disorder. Charney & Nestler's Neurobiology of Mental Illness, pp. 979-999. Oxford University Press.

Faraone, S. V. & Radonjić, N. V. (In press). Neurobiology of Attention-Deficit/Hyperactivity Disorder. In Tasman's Psychiatry 5th edition (ed. R. M. B. In: Tasman A., Schulze T.G., Ng C.H., Alfonso C.A., Lecic-Tosevski D., Kanba S., Alarcón R.D. and Ndetei D.M. (Eds)). Springer Nature, Switzerland.

[190] Faraone, S. V., Spencer, T. J., Madras, B. K., Zhang-James, Y., & Biederman, J. (2014). Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: A meta-analysis. *Molecular Psychiatry*, *19*(8), 880-889.

[191] Faraone, S. V., Bhide, P. G., & Biederman, J. (2018). Neurobiology of attention deficit hyperactivity disorder. Animal and human studies. *Charney & Nestler's Neurobiology of Mental Illness*, pp. 865-878. Oxford University Press.

especially those that do not address the dopamine transporter, cannot support a causal connection between maternal use of acetaminophen during pregnancy and offspring ADHD.

156. Plaintiffs' experts' attempt to link physiological findings in rodents to ADHD in humans is also inconsistent with the general understanding that there is a fundamental disconnect between rodent and human disease. For example, a 2005 review entitled "Cancer in rodents: does it tell us about cancer in humans?," by Anisimov et al. explains:

a. "Whereas laboratory rodents (namely mice and rats) are similar to humans in some aspects, there are important differences among mammalian species that make valid interpretation and extrapolation of the results from rodent cancer experiments to humans problematic."

b. "The spontaneous regression of tumours is a rare phenomenon in adult humans, whereas it is common in mature laboratory rodents."

c. "Few rodent carcinogens were established as clearly carcinogenic to humans. Similarly, some human carcinogens are not carcinogenic to rodents. This creates a significant problem for interpreting the results of animal experiments with carcinogens in relation to humans."

d. "These and other differences warn against the simple extrapolation of the results of rodent experiments to humans and call for further investigation of this important problem to reliably predict cancer risks, as well as foster success in treating human cancers based on data from laboratory animal studies."[192]

[192] Anisimov, V. N., Ukraintseva, S. V., & Yashin, A. I. (2005). Cancer in rodents: Does it tell us about cancer in humans?. *Nature Reviews Cancer*, *5*(10), 807-819.

157. Attempting to extrapolate from findings from rodent studies to make conclusions about ADHD in humans is even more problematic. While cancer is often caused by a single genetic mutation, either inherited or occurring through carcinogens, ADHD's genetic etiology is extremely complex. Researchers estimate that approximately 7,000 genomic loci are involved in the etiology of ADHD but only 27 have been described with certainty. Compared with cancer, the etiology and pathophysiology of ADHD is very poorly understood. Because extrapolating the results of rodent experiments to humans is problematic in studying cancer,[193] it is even less appropriate with respect to determining causation with respect to ADHD.

158. Finally, rodent studies have not been successful in developing new treatments or diagnostic methods or ADHD or, for that matter, any clinically actionable event that is useful in the management of ADHD, raising serious questions about their usefulness in this context. To the contrary, rodent studies have impeded the treatment of ADHD, with studies of the medications for ADHD inaccurately concluding that those medications would lead to addiction in ADHD youth treated with those medications.[194] This view was discredited when human studies documented that the medications used for ADHD did not increase the risk for substance use disorders but instead decreased that risk.[195]

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[193] Anisimov, V. N., Ukraintseva, S. V., & Yashin, A. I. (2005). Cancer in rodents: Does it tell us about cancer in humans?. *Nature Reviews Cancer*, *5*(10), 807-819.

[194] Kuczenski, R., & Segal, D. S. (2002). Exposure of adolescent rats to oral methylphenidate: Preferential effects on extracellular norepinephrine and absence of sensitization and cross-sensitization to methamphetamine. *Journal of Neuroscience*, *22*(16), 7264-7271.

dela Pena, I., & Cheong, J. H. (2013). Abuse and dependence liability analysis of methylphenidate in the spontaneously hypertensive rat model of attention-deficit/hyperactivity disorder (ADHD): What have we learned?. *Archives of Pharmacal Research*, *36*, 400-410.

Kuczenski, R. & Segal, D. S. (1994). Neurochemistry of amphetamine. *Amphetamine and Its Analogs: Psychopharmacology, Toxicology, and Abuse*, pp. 81-113. Academic Press, Inc.

[195] Faraone, S. V., & Wilens, T. E. (2007). Effect of stimulant medications for attention-deficit/hyperactivity disorder on later substance use and the potential for stimulant misuse, abuse, and diversion. *Journal of Clinical Psychiatry*, *68*(Suppl 11), 15-22.

159. In short, observations of physiological changes in or properties of the rodent brain following acetaminophen exposure do not constitute reliable evidence that in utero exposure to humans is capable of affecting the much more complicated structures of the human brain that control advanced cognitive functions relevant to ADHD.

### iii. Rodent Studies Do Not Demonstrate a Biological Mechanism by Which Acetaminophen Causes ADHD

160. Rodent studies also do not demonstrate a plausible biological mechanism by which acetaminophen caused ADHD. Plaintiffs' expert Dr. Hollander proposes a number of potential mechanisms whereby acetaminophen exposure in utero could cause ADHD, including: oxidative stress, epigenetic effects, excess NAPQI formation, effects on the prostaglandin system, endocannabinoid dysfunction, endocrine dysfunction, and altered brain-derived neurotrophic factor.[196] Dr. Baccarelli's report lists similar potential causal mechanisms.[197] But the relevant literature does not support a finding that any of these purported mechanisms are plausible. Rather, they are mere hypotheses.

161. While certain studies cited by plaintiff experts speculate that acetaminophen causes oxidative stress that results in ADHD, this is an unproven hypothesis. Philippot et al. (2022)

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Faraone, S. V., Rostain, A. L., Montano, C. B., Mason, O., Antshel, K. M., & Newcorn, J. H. (2020). Systematic review: Nonmedical use of prescription stimulants: Risk factors, outcomes, and risk reduction strategies. *Journal of the American Academy of Child & Adolescent Psychiatry*, *59*(1), 100-112.

Groenman, A. P., Janssen, T. W., & Oosterlaan, J. (2017). Childhood psychiatric disorders as risk factor for subsequent substance abuse: A meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(7), 556-569.

Humphreys, K. L., Eng, T., & Lee, S. S. (2013). Stimulant medication and substance use outcomes: A meta-analysis. *JAMA Psychiatry*, *70*(7), 740-749.

Wilens, T. E., Faraone, S. V., Biederman, J., & Gunawardene, S. (2003). Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*, *111*(1), 179-185.

[196] Hollander Amended Rep. at 75-87.

[197] Baccarelli Amended Rep. at 44-51.

report acute oxidative stress in the hippocampus of mouse after neonatal acetaminophen exposure. They state: "Oxidative stress and inflammatory responses have been implicated in the etiology of ADHD and ASD, as indicated by differential expression of pro-inflammatory cytokines."[198] But these pathways remain theoretical, as recently acknowledged by Misiak et al. (2022):

> "In conclusion, findings from this meta-analysis indicate that individuals with ADHD might show subclinical immune-inflammatory alterations in terms of elevated levels of IL-6 and reduced levels of TNF-α. However, larger studies recording potential confounding factors and comorbid mental disorders are needed to provide more insights into the role of inflammation in the pathophysiology of ADHD. Moreover, longitudinal and interventional studies are warranted to disentangle whether altered immune-inflammatory responses are causally associated with the development of ADHD."[199]

162. In addition, the theory that acetaminophen causes oxidative stress that can lead to ADHD is contradicted by studies showing that acetaminophen reduces oxidative stress in the brain and has neuroprotective effects. The study of Tripathy and Grammas, for example, showed that acetaminophen protected brain cells from oxidative stress, concluding: "These data show that acetaminophen has anti-oxidant and anti-inflammatory effects on the cerebrovasculature and suggest a heretofore unappreciated therapeutic potential for this drug in neurodegenerative diseases such as Alzheimer's disease that are characterized by oxidant and inflammatory stress."[200] Thus, the literature on acetaminophen and oxidative stress is at best contradictory.[201]

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[198] Philippot, G., Hosseini, K., Yakub, A., Mhajar, Y., Hamid, M., Buratovic, S., & Fredriksson, R. (2022). Paracetamol (acetaminophen) and its effect on the developing mouse brain. *Frontiers in Toxicology*, *4*, 867748.

[199] Misiak, B., Wojta-Kempa, M., Samochowiec, J., Schiweck, C., Aichholzer, M., Reif, A., ... & Stańczykiewicz, B. (2022). Peripheral blood inflammatory markers in patients with attention deficit/hyperactivity disorder (ADHD): A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *118*, 110581.

[200] Tripathy, D., & Grammas, P. (2009). Acetaminophen protects brain endothelial cells against oxidative stress. *Microvascular Research*, *77*(3), 289-296.

[201] Bührer, C., Endesfelder, S., Scheuer, T., & Schmitz, T. (2021). Paracetamol (acetaminophen) and the developing brain. *International Journal of Molecular Sciences*, *22*(20), 11156.

163. Plaintiffs' experts' assertion that epigenetic effects are a plausible causal mechanism is similarly speculative. Epigenetic effects are the biological mechanism whereby any environmental event modifies how genes are expressed in cells. These effects are part of the normal biology of the cell. Both toxic and non-toxic exposures cause epigenetic changes. Thus, the claim that epigenetics causes ADHD is as nonspecific as saying that any environmental effect causes ADHD. None of plaintiffs' experts has described an epigenetic mechanism (e.g., DNA methylation, histone modification, chromatin remodeling of a specific gene or genes) that is plausibly involved in the putative association between acetaminophen and ADHD. While Dr. Hollander notes that one study found that acetaminophen caused epigenetic changes in cord blood that involved genes regulating oxidative stress, that study did not show that those changes led to subsequent ADHD.[202] Moreover, data from the Norwegian Mother, Father and Child Cohort Study and the Medical Birth Registry of Norway, Olstad et al. (2023) did not find any effect of prenatal acetaminophen exposure on cord blood DNA Methylation in ADHD children.[203]

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Lalert, L., Ji-Au, W., Srikam, S., Chotipinit, T., Sanguanrungsirikul, S., Srikiatkhachorn, A., & Maneesri-le Grand, S. (2020). Alterations in synaptic plasticity and oxidative stress following long-term paracetamol treatment in rat brain. *Neurotoxicity Research*, *37*, 455-468.

Tripathy, D., & Grammas, P. (2009). Acetaminophen protects brain endothelial cells against oxidative stress. *Microvascular Research*, *77*(3), 289-296.

Tripathy, D., & Grammas, P. (2009). Acetaminophen inhibits neuronal inflammation and protects neurons from oxidative stress. *Journal of Neuroinflammation*, *6*, 1-9.

Tripathy, D., Sanchez, A., Yin, X., Martinez, J., & Grammas, P. (2012). Age-related decrease in cerebrovascular-derived neuroprotective proteins: Effect of acetaminophen. *Microvascular Research*, *84*(3), 278-285.

Lalert, L., le-Grand, S. M., Techarang, T., Huntula, S., & Punsawad, C. (2022). Neuroprotective effect of low-dose paracetamol treatment against cognitive dysfunction in d-galactose-induced aging mice. *Heliyon*, *8*(10), e11108.

[202] Hollander Amended Rep. at 85 (citing Gervin et al., 2017).

Gervin, K., Nordeng, H., Ystrom, E., Reichborn-Kjennerud, T., & Lyle, R. (2017). Long-term prenatal exposure to paracetamol is associated with DNA methylation differences in children diagnosed with ADHD. *Clinical Epigenetics*, *9*(1), 1-9.

[203] Olstad, E. W., Nordeng, H. M. E., Lyle, R., & Gervin, K. (2023). No impact of prenatal paracetamol and folic acid exposure on cord blood DNA methylation in children with attention-deficit/hyperactivity disorder. *Frontiers in Genetics*, *14*, 1204879.

164. None of the other mechanisms identified by plaintiffs' experts is plausible because none has been documented to play a role in the etiology or pathophysiology of ADHD. Plaintiffs' experts' logic seems to be that acetaminophen can cause changes to the brain in several biological systems and, because these biological systems are involved in the brain and the brain is involved in ADHD, any of them are plausible mechanisms for causing ADHD. But if that were the case, one could claim that any brain disorder is caused by acetaminophen without additional evidence.

165. I do not agree that any of the identified potential mechanisms are plausible because, after decades of neurobiological research, none has been shown to be involved in the etiology or pathophysiology of ADHD. I have reviewed in depth data from the largest and most definitive biological study of ADHD ever conducted, i.e., the genomewide study of ADHD that I had the privilege of leading for many decades. This definitive genomic study is based on interrogating the genomes of 38,691 individuals with ADHD and 186,843 controls using the method of genomewide association.[204] This method allows one to discover which genes and biological pathways are involved in the etiology of ADHD. Dr. Baccarelli's report states: "The recognized potential mechanisms that support biologic plausibility include (1) excess production of toxic metabolite NAPQI; (2) oxidative stress, inflammation, immune reaction; (3) reduced production of prostaglandin; (4) endocannabinoid dysfunction; (5) alterations in BDNF production and distribution; (6) endocrine disruption; and (7) epigenetic changes." Dr. Hollander's report refers to the same mechanisms. None of the first six mechanisms proposed by the plaintiff experts emerged as being relevant to the genomic etiology of ADHD. The seventh was not addressed by

[204] Demontis, D., Walters, G. B., Athanasiadis, G., Walters, R., Therrien, K., Nielsen, T. T., ... & Børglum, A. D. (2023). Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. *Nature Genetics*, *55*(2), 198-208.

our study as we did not assess epigenetic changes. Instead of the plaintiff's mechanisms, the study implicated genes encoding integral components of the postsynaptic density membrane and especially genes expressed in the frontal cortex and in early brain development. The genes implicated in ADHD were expressed in brain specific neuronal sub-types, most notably midbrain dopaminergic neurons. If the mechanisms proposed by the plaintiff experts were plausibly involved in ADHD, they would have been detected in the genome-wide study; they were not.

**E. Dr. Bauer's So-Called "Consensus Statement" Does Not Support A Causal Inference.**

166. Several of plaintiffs' experts rely heavily on an editorial drafted by 13 scientists, and signed by 78 others, in the journal Nature Reviews Endocrinology.[205] Although the authors gave this editorial the misleading title "Consensus Statement," it is not endorsed by, and does not reflect the views of, any "regulatory authorities or medical specialty organizations."[206] In fact, the relevant professional societies from all across the world sharply criticized it,[207] as did responses in the same journal.[208]

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[205] Bauer, A., Swan, S., Kriebel, D., Liew Z., Taylor H., Bornehag, C.-G., … & Kristensen, D. (2021). Paracetamol use during pregnancy – a call for precautionary action. *Nature Reviews Endocrinology, 17,* 757-766.

[206] European Network of Teratology Information Services (2021). ENTIS: Position statement on acetaminophen (paracetamol) in pregnancy, https://www.entis-org.eu/wp-content/uploads/2021/10/ENTIS-position-statement-on-acetaminophen-3.10.2021.pdf.

[207] Id. (evidence "is weak, inconsistent and to a large extent fundamentally flawed); American College of Gynecology (2021).

ACOG response to consensus statement on paracetamol use during pregnancy, https://www.acog.org/news/news-articles/2021/09/response-to-consensus-statement-on-paracetamol-use-during-pregnancy ("no clear evidence).

Hutson, J. R., Smith, G. N., Codsi, E., & Garcia-Bournissen, F. (2021). Statement on the use of acetaminophen for analgesia and fever in pregnancy. The Society of Obstetricians and Gynaecologists of Canada.

[208] Alwan S., Conover E., Harris-Sagaribay L., Lamm S., Lavigne, S., Lusskin, S. … & Wisner K (2022). Paracetamol use during pregnancy – caution over causal inference from available data. *Endocrinology, 18,* 190.

Damaker, P., Cleary B., Webb-Schoendorfer C., Shecthman S., Cassina M., Panchaud A. & Diav-Cirtin O (2022). Handle with care – interpretation, synthesis and fissemination of data on paractamol in pregnancy. *Nature Reviews Endocrinology, 18,* 191

167. Even taken at face value, the "Consensus Statement" did not break any new ground or offer any additional evidence, beyond that which I have already reviewed here. It highlighted, as I have, the fact that studies had "identified positive associations [between] APAP exposure and a range of clinically assessed and parent-reported neuro-developmental outcomes, primarily" ADHD.[209] But it pointedly refused to adopt the position taken by plaintiffs' experts. In a follow-up letter responding to critics, the authors noted that because they "agree that limitations uncertainties remain," they "avoided any inference of causality."[210] They also acknowledged that "for fever and severe pain during pregnancy [acetaminophen] is a necessary and appropriate treatment.[211] The authors simply called for "precaution" and in particular for the conduct of more "epidemiological and experimental studies."[212]

## VII.

## BRADFORD-HILL CRITERIA FOR CAUSALITY

168. The Bradford Hill criteria were developed by the epidemiologist Sir Austin Bradford Hill to determine whether an observed association between an exposure and a disease indicates a causal relationship.[213] It is my understanding that another expert in the specialty of epidemiology will provide a more complete analysis of the Bradford Hill criteria in connection

[209] Bauer, A., Swan, S., Kriebel, D., Liew Z., Taylor H., Bornehag, C.-G., … & Kristensen, D. (2021). Paracetamol use during pregnancy – a call for precautionary action. *Nature Reviews Endocrinology, 17*, 757-766.

[210] Bauer, A., Swan, S., Kriebel, D., Liew Z., Taylor H., Bornehag, C.-G., … & Kristensen, D. (2022). Reply to 'Paracetimol use in pregnancy – caution over causal inference from available data'; 'Handle with care – interpretation, synthesis and dissemination of data on paracetamol in pregnancy.' *Nature Reviews Endocrinology, 18*, 192.

[211] Id.

[212] Bauer, A., Swan, S., Kriebel, D., Liew Z., Taylor H., Bornehag, C.-G., … & Kristensen, D. (2021). Paracetamol use during pregnancy – a call for precautionary action. *Nature Reviews Endocrinology, 17*, 757-766.

[213] Fedak, K. M., Bernal, A., Capshaw, Z. A., & Gross, S. (2015). Applying the Bradford Hill criteria in the 21st century: How data integration has changed causal inference in molecular epidemiology. *Emerging Themes in Epidemiology, 12*, 1-9.

with the posited association here, but I am familiar with the Bradford Hill approach and believe it is important to note that application of its key criteria to the potential association between in utero exposure to acetaminophen and ADHD does not support a causal relationship.

a. **Strength of association:** The stronger the association between two variables, the more likely it is that there is a causal relationship. As I explained above, the data demonstrate that there is no valid association between in utero acetaminophen exposure and offspring ADHD. The studies that report an association all computed weak risk ratios that are likely the result of genetic confounding, other sources of confounding, and other methodological problems. The published pooled risk ratios from meta-analyses are very low and are similarly explained by established familial/genetic confounding factors. The risk ratio disappears when familial confounding is controlled. Thus, the strength of association criterion is not met.

b. **Consistency:** As association is consistent if it is observed in multiple studies using different methods and in different populations. The epidemiological studies are not consistent. The cohort and case-control observational studies that have assessed the association between maternal use of acetaminophen during pregnancy and offspring ADHD have yielded inconsistent results. The association does not exist when using the sibling control design, which controls for familial/genetic confounding. Moreover, if a consistent association exists, the population studies should reveal an increase in the prevalence of ADHD with the introduction of acetaminophen across geographic regions, and the prevalence of ADHD should co-vary with the prevalence of acetaminophen use during pregnancy. The data do not bear this out. Plaintiff expert Dr. Cabrera concedes that "the evidence is not

consistent across all studies, and some studies did not find significant associations or found mixed results."[214] The consistency criterion is not supported.

c. **Specificity:** A relationship should be specific to the exposure and the outcome to infer causation. No study purporting to observe an association between in utero acetaminophen exposure and offspring ADHD has documented that this association is specific to ADHD, as opposed to other conditions. To the contrary, plaintiffs' experts assert that the acetaminophen exposure under consideration is linked to other conditions that are very different from ADHD, including ASD. Dr. Hollander treats various neurodevelopmental disorders as if they were a single disorder and attempts to lump together data relating to these varying disorders as evidence of causation with respect to each one individually. The specificity criterion is not met.

d. **Temporality:** The exposure should precede the outcome in time. Maternal use of acetaminophen during pregnancy necessarily precedes the onset of any symptoms of ADHD in offspring who are subsequently born. It is unknown, however, if maternal use of acetaminophen precedes the undefined pathophysiology in the brain that develops throughout gestation and causes the onset of ADHD symptoms after birth. Because there is evidence that ADHD is strongly influenced by the DNA of the fetus, it is biologically plausible that the causal pathophysiology of ADHD occurs before maternal use of acetaminophen. In fact, the data from DNA studies suggest that it is the genomic risk for ADHD shared by the mother and fetus that leads to acetaminophen use. The temporality criterion is not established.

[214] Cabrera Amended Rep. at 160.

e. **Biological gradient:** An exposure-response relationship should be observed where the risk of the outcome increases with increasing exposure to the potential cause. An exposure-response (otherwise known as dose-response) relationship has been observed in some studies but not in the sibling-control study, which strongly suggests that any observed dose-response is due to familial confounding. The studies of dose response are also subject to other confounding factors and methodological problems. The biological gradient criterion is not supported.

f. **Plausibility:** The observed association should be biologically plausible, based on what is known about the disease and the exposure. According to Fedak et al. (2015),[215] "Hill's criterion of plausibility is satisfied if the relationship is consistent with the current body of knowledge regarding the etiology and mechanism of disease." Because there is currently no definitive description of any pathologic mechanism that explains the onset and symptoms of ADHD, there is no basis to conclude that there is a plausible biological mechanism by which in utero acetaminophen exposure causes ADHD. Moreover, the mechanisms proposed by the plaintiffs' experts are not plausible because, as explained, the largest and most definitive biological study of ADHD did not detect them as being involved in the etiology of ADHD. The plausibility criterion is not satisfied.

g. **Experiment:** This consideration asks whether the effect is demonstrable in experimental settings, such as in animal models, or whether disease risk declines following an intervention or cessation of exposure. Animal model studies that

[215] Fedak, K. M., Bernal, A., Capshaw, Z. A., & Gross, S. (2015). Applying the Bradford Hill criteria in the 21st century: How data integration has changed causal inference in molecular epidemiology. *Emerging Themes in Epidemiology*, *12*, 1-9.

observe an association between fetal acetaminophen exposure and supposed proxy behaviors for ADHD are flawed and unreliable. As I explain earlier in this report, it is not possible to diagnose ADHD in rodents because the rodent brain is very different from the human brain, especially in regions regulating the complex behaviors of ADHD. In addition, many rodent behaviors that plaintiffs' experts claim are indicative of ADHD have no actual connection to the symptoms of the disorder.

h. **Coherence**: The observed association should also be consistent with what is known about the natural history and biology of the disease being studied. As I noted earlier, plaintiffs' experts' theories are not supported by data on the prevalence of ADHD in countries with greater or lesser acetaminophen use by pregnant women. Accordingly, the data are not coherent.

i. **Analogy**: Under this factor, an association should be similar to other known causal relationships. According to Fedak et al. (2015), "Analogy has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way." There is no evidence of a causal relationship between maternal exposure to APAP and any outcome that is similar to ADHD. Thus, this factor is not satisfied either.

The opinions in this report are based upon my education, training, and professional experience, as well as on my review of published literature and other materials cited in this report and in the accompanying Materials Reference List and are expressed to a reasonable degree of medical and scientific certainty or probability.

I will review additional data and information on this matter as they become available.

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Stephen V. Faraone, Ph.D.
8/22/2023